(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 November 2004 (25.11.2004)

PCT

(10) International Publication Number
WO 2004/101522 A1

(51) International Patent Classification[7]: C07D 211/70, 417/06, 401/06, A61K 31/435, 31/444, 31/4427, A61P 25/04, 25/22

(21) International Application Number: PCT/GB2004/002074

(22) International Filing Date: 13 May 2004 (13.05.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0301444-6	16 May 2003 (16.05.2003)	SE
0400024-6	9 January 2004 (09.01.2004)	SE

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

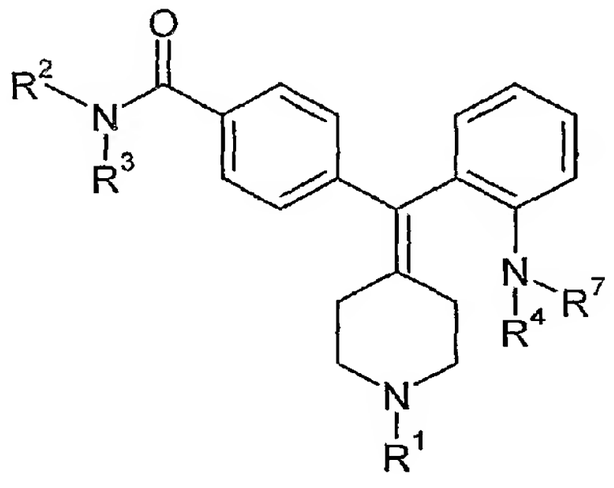
Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DIARYLMETHYLIDENE PIPERIDINE DERIVATIVES, PREPARATIONS THEREOF AND USES THEREOF



(IA)

(57) Abstract: Compounds of formula: (I) wherein R^1, R^2, R^3, R^4 and R^7 are as defined in the specification, as well as salts, enantiomers thereof and pharmaceutical compositions including the compounds are prepared. They are useful in therapy, in particular in the management of pain.

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DIARYLMETHYLIDENE PIPERIDINE DERIVATIVES, PREPARATIONS THEREOF AND USES THEREOF

FIELD OF THE INVENTION

The present invention is directed to novel compounds, to a process for their preparation, their use and pharmaceutical compositions comprising the novel compounds. The novel compounds are useful in therapy, and in particular for the treatment of pain, anxiety and functional gastrointestinal disorders.

BACKGROUND OF THE INVENTION

The δ receptor has been identified as having a role in many bodily functions such as circulatory and pain systems. Ligands for the δ receptor may therefore find potential use as analgesics, and/or as antihypertensive agents. Ligands for the δ receptor have also been shown to possess immunomodulatory activities.

The identification of at least three different populations of opioid receptors (μ, δ and κ) is now well established and all three are apparent in both central and peripheral nervous systems of many species including man. Analgesia has been observed in various animal models when one or more of these receptors has been activated.

With few exceptions, currently available selective opioid δ ligands are peptidic in nature and are unsuitable for administration by systemic routes. One example of a non-peptidic δ-agonist is SNC80 (Bilsky E.J. et al., Journal of Pharmacology and Experimental Therapeutics, 273(1), pp. 359-366 (1995)).

Many δ agonist compounds that have been identified in the prior art have many disadvantages in that they suffer from poor pharmacokinetics and are not analgesic when administered by systemic routes. Also, it has been documented that many of these δ agonist compounds show significant convulsive effects when administered systemically.

U.S. Patent No. 6,187,792 to Delorme et al. describes some δ-agonists.

However, there is still a need for improved δ-agonists.

DESCRIPTION OF THE INVENTION

Unless specified otherwise within this specification, the nomenclature used in this specification generally follows the examples and rules stated in *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H*, Pergamon Press, Oxford, 1979, which is incorporated by references herein for its exemplary chemical structure names and rules on naming chemical structures.

The term "C_{m-n}" or "C_{m-n} group" used alone or as a prefix, refers to any group having m to n carbon atoms.

The term "hydrocarbon" used alone or as a suffix or prefix, refers to any structure comprising only carbon and hydrogen atoms up to 14 carbon atoms.

The term "hydrocarbon radical" or "hydrocarbyl" used alone or as a suffix or prefix, refers to any structure as a result of removing one or more hydrogens from a hydrocarbon.

The term "alkyl" used alone or as a suffix or prefix, refers to monovalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms.

The term "alkylene" used alone or as suffix or prefix, refers to divalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms, which serves to links two structures together.

The term "alkenyl" used alone or as suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 2 up to about 12 carbon atoms.

The term "alkynyl" used alone or as suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon triple bond and comprising at least 2 up to about 12 carbon atoms.

The term "cycloalkyl," used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms.

The term "cycloalkenyl" used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 3 up to about 12 carbon atoms.

The term "cycloalkynyl" used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon triple bond and comprising about 7 up to about 12 carbon atoms.

The term "aryl" used alone or as suffix or prefix, refers to a monovalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*, 4n + 2 delocalized electrons) and comprising 5 up to about 14 carbon atoms.

The term "arylene" used alone or as suffix or prefix, refers to a divalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*, 4n + 2 delocalized electrons) and comprising 5 up to about 14 carbon atoms, which serves to link two structures together.

The term "heterocycle" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s). Heterocycle may be saturated or unsaturated, containing one or more double bonds, and heterocycle may contain more than one ring. When a heterocycle contains more than one ring, the rings may be fused or unfused. Fused rings generally refer to at least two rings share two atoms therebetween. Heterocycle may have aromatic character or may not have aromatic character.

The term "heteroaromatic" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and

including at least 3 and up to about 20 atoms in the ring(s), wherein the ring-containing structure or molecule has an aromatic character (*e.g.*, 4n + 2 delocalized electrons).

The term "heterocyclic group," "heterocyclic moiety," "heterocyclic," or "heterocyclo" used alone or as a suffix or prefix, refers to a radical derived from a heterocycle by removing one or more hydrogens therefrom.

The term "heterocyclyl" used alone or as a suffix or prefix, refers a monovalent radical derived from a heterocycle by removing one hydrogen therefrom.

The term "heterocyclylene" used alone or as a suffix or prefix, refers to a divalent radical derived from a heterocycle by removing two hydrogens therefrom, which serves to links two structures together.

The term "heteroaryl" used alone or as a suffix or prefix, refers to a heterocyclyl having aromatic character.

The term "heterocylcoalkyl" used alone or as a suffix or prefix, refers to a heterocyclyl that does not have aromatic character.

The term "heteroarylene" used alone or as a suffix or prefix, refers to a heterocyclylene having aromatic character.

The term "heterocycloalkylene" used alone or as a suffix or prefix, refers to a heterocyclylene that does not have aromatic character.

The term "six-membered" used as prefix refers to a group having a ring that contains six ring atoms.

The term "five-membered" used as prefix refers to a group having a ring that contains five ring atoms.

A five-membered ring heteroaryl is a heteroaryl with a ring having five ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary five-membered ring heteroaryls are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4- oxadiazolyl.

A six-membered ring heteroaryl is a heteroaryl with a ring having six ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

The term "substituted" used as a prefix refers to a structure, molecule or group, wherein one or more hydrogens are replaced with one or more $C_{1\text{-}6}$hydrocarbon groups, or one or more chemical groups containing one or more heteroatoms selected from N, O, S, F, Cl, Br, I, and P. Exemplary chemical groups containing one or more heteroatoms include $-NO_2$, -OR, -Cl, -Br, -I, -F, $-CF_3$, -C(=O)R, -C(=O)OH, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $-SO_3H$, $-SO_2R$, -S(=O)R, -CN, -OH, -C(=O)OR, $-C(=O)NR_2$, -NRC(=O)R, oxo (=O), imino (=NR), thio (=S), and oximino (=N-OR), wherein each "R" is a $C_{1\text{-}6}$hydrocarbyl. For example, substituted phenyl may refer to nitrophenyl, methoxyphenyl, chlorophenyl, aminophenyl, etc., wherein the nitro, methoxy, chloro, and amino groups may replace any suitable hydrogen on the phenyl ring.

The term "substituted" used as a suffix of a first structure, molecule or group, followed by one or more names of chemical groups refers to a second structure, molecule or group, which is a result of replacing one or more hydrogens of the first structure, molecule or group with the one or more named chemical groups. For example, a "phenyl substituted by nitro" refers to nitrophenyl.

Heterocycle includes, for example, monocyclic heterocycles such as: aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazoline, dioxolane, sulfolane 2,3-dihydrofuran, 2,5-dihydrofuran tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydro-pyridine, piperazine, morpholine, thiomorpholine, pyran, thiopyran, 2,3-dihydropyran, tetrahydropyran, 1,4-dihydropyridine, 1,4-dioxane, 1,3-dioxane, dioxane, homopiperidine, 2,3,4,7-tetrahydro-1*H*-azepine homopiperazine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin, and hexamethylene oxide.

In addition, heterocycle includes aromatic heterocycles, for example, pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, furazan, pyrrole, imidazole, thiazole, oxazole, pyrazole, isothiazole, isoxazole, 1,2,3-triazole, tetrazole, 1,2,3-thiadiazole, 1,2,3-oxadiazole, 1,2,4-triazole, 1,2,4-thiadiazole, 1,2,4-oxadiazole, 1,3,4-triazole, 1,3,4-thiadiazole, and 1,3,4-oxadiazole.

Additionally, heterocycle encompass polycyclic heterocycles, for example, indole, indoline, isoindoline, quinoline, tetrahydroquinoline, isoquinoline, tetrahydroisoquinoline, 1,4-benzodioxan, coumarin, dihydrocoumarin, benzofuran, 2,3-dihydrobenzofuran, isobenzofuran, chromene, chroman, isochroman, xanthene, phenoxathiin, thianthrene, indolizine, isoindole, indazole, purine, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, phenanthridine, perimidine, phenanthroline, phenazine, phenothiazine, phenoxazine, 1,2-benzisoxazole, benzothiophene, benzoxazole, benzthiazole, benzimidazole, benztriazole, thioxanthine, carbazole, carboline, acridine, pyrolizidine, and quinolizidine.

In addition to the polycyclic heterocycles described above, heterocycle includes polycyclic heterocycles wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidine, diazabicyclo[2.2.1]heptane and 7-oxabicyclo[2.2.1]heptane.

Heterocyclyl includes, for example, monocyclic heterocyclyls, such as: aziridinyl, oxiranyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, dioxolanyl, sulfolanyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, tetrahydrofuranyl, thiophanyl, piperidinyl, 1,2,3,6-tetrahydro-pyridinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-1*H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-1,3-dioxepinyl, and hexamethylene oxidyl.

In addition, heterocyclyl includes aromatic heterocyclyls or heteroaryl, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, furazanyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4 oxadiazolyl.

Additionally, heterocyclyl encompasses polycyclic heterocyclyls (including both aromatic or non-aromatic), for example, indolyl, indolinyl, isoindolinyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, 1,4-benzodioxanyl, coumarinyl, dihydrocoumarinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, isobenzofuranyl, chromenyl, chromanyl, isochromanyl, xanthenyl, phenoxathiinyl, thianthrenyl, indolizinyl, isoindolyl, indazolyl, purinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, phenanthridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxazinyl, 1,2-benzisoxazolyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrolizidinyl, and quinolizidinyl.

In addition to the polycyclic heterocyclyls described above, heterocyclyl includes polycyclic heterocyclyls wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidinyl, diazabicyclo[2.2.1]heptyl; and 7-oxabicyclo[2.2.1]heptyl.

The term "alkoxy" used alone or as a suffix or prefix, refers to radicals of the general formula –O-R, wherein R is selected from a hydrocarbon radical. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy, cyclopropylmethoxy, allyloxy, and propargyloxy.

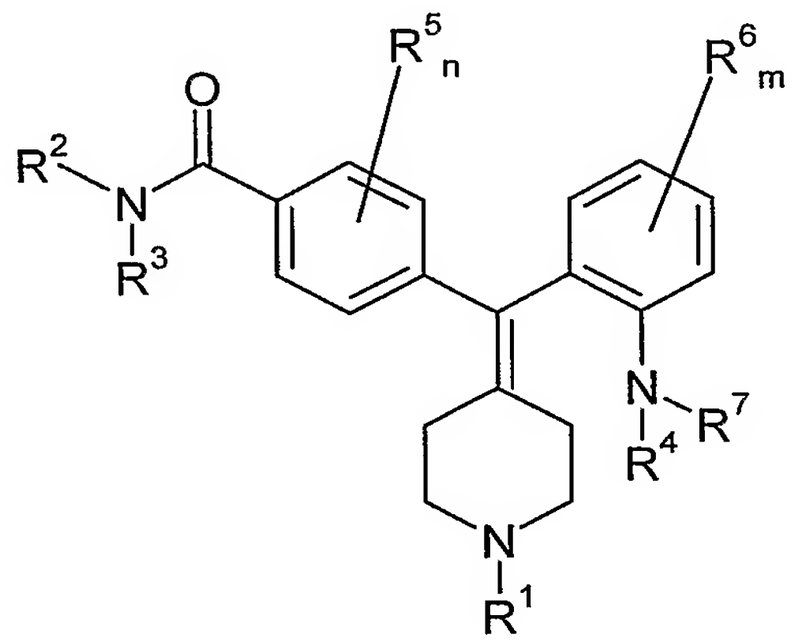
The term "amine" or "amino" used alone or as a suffix or prefix, refers to radicals of the general formula –NRR', wherein R and R' are independently selected from hydrogen or a hydrocarbon radical.

Halogen includes fluorine, chlorine, bromine and iodine.

"Halogenated," used as a prefix of a group, means one or more hydrogens on the group is replaced with one or more halogens.

"RT" or "rt" means room temperature.

In one aspect, the invention provides a compound of formula I, a pharmaceutically acceptable salt thereof, diastereomers thereof, enantiomers thereof, and mixtures thereof:



I

wherein

R^1 is selected from hydrogen, C_{1-6}alkyl-O-C(=O)-, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted C_{6-10}aryl, optionally substituted C_{2-9}heterocyclyl, optionally substituted C_{6-10}aryl-C_{1-3}alkyl and optionally substituted C_{2-9}heterocyclyl-C_{1-3}alkyl;

n is 0, 1 or 2; m is 0, 1, or 2;

R^2, R^3 and R^4 are, independently, selected from hydrogen, optionally substituted C_{1-6}alkyl, and optionally substituted C_{3-6}cycloalkyl;

R^5 and R^6 are, independently, selected from -R, $-NO_2$, -OR, -Cl, -Br, -I, -F, $-CF_3$, -C(=O)R, -C(=O)OH, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $-SO_3H$, $-SO_2R$, -S(=O)R,

-CN, -OH, -C(=O)OR, -C(=O)NR_2, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen or C_{1-6}alkyl; and

R^7 is selected from –H, -OH, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted C_{6-10}aryl, optionally substituted C_{2-9}heterocyclyl, optionally substituted C_{6-10}aryl-C_{1-6}alkyl, optionally substituted C_{2-9}heterocyclyl-C_{1-6}alkyl, -C(=O)-NR^8R^9, –C(=O)-O-R^8, –S(=O)-R^8, –$S(=O)_2$-R^8, -C(=O)-R^8 and -SO_3H, wherein R^8 and R^9 are independently selected from –H, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted C_{6-10}aryl, optionally substituted C_{2-9}heterocyclyl, optionally substituted C_{6-10}aryl-C_{1-6}alkyl, and optionally substituted C_{2-9}heterocyclyl-C_{1-6}alkyl.

Particularly, the compounds of the present invention are those of formula I, wherein R^1 is selected from hydrogen, C_{1-6}alkyl-O-C(=O)-, optionally substituted C_{1-6}alkyl, and optionally substituted C_{3-6}cycloalkyl;

R^2 and R^3 are ethyl;

R^4 is selected from hydrogen and C_{1-3}alkyl;

R^7 is selected from –H, -OH, optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl, optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted C_{3-6}cycloalkyl-C_{1-3}alkyl, -C(=O)-N-R^8R^9, –C(=O)-O-R^8, –S(=O)-R^8, –$S(=O)_2$-R^8, -C(=O)-R^8 and -SO_3H, wherein R^8 and R^9 are independently selected from –H, optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl, optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted C_{3-6}cycloalkyl-C_{1-3}alkyl; and

n and m are 0.

More particularly, the compounds of the present invention are those of formula I, wherein R^1 is selected from hydrogen and C_{1-6}alkyl-O-C(=O)-;

R^2 and R^3 are ethyl;

R^4 is selected from hydrogen and methyl;

R^7 is selected from –H, phenyl-C_{1-3}alkyl, C_{3-6}cycloalkyl-C_{1-3}alkyl, C_{3-6}cycloalkyl, phenyl, optionally substituted C_{1-6}alkyl, -C(=O)-N-R^8R^9, –S(=O)$_2$-R^8, and -C(=O)-R^8, wherein R^8 and R^9 are independantly selected from –H, phenyl-C_{1-3}alkyl, C_{3-6}cycloalkyl-C_{1-3}alkyl, C_{3-6}cycloalkyl, phenyl, and optionally substituted C_{1-6}alkyl; and

n and m are 0.

Most particularly, the compounds of the present invention are those of formula I, wherein

R^1 is hydrogen;

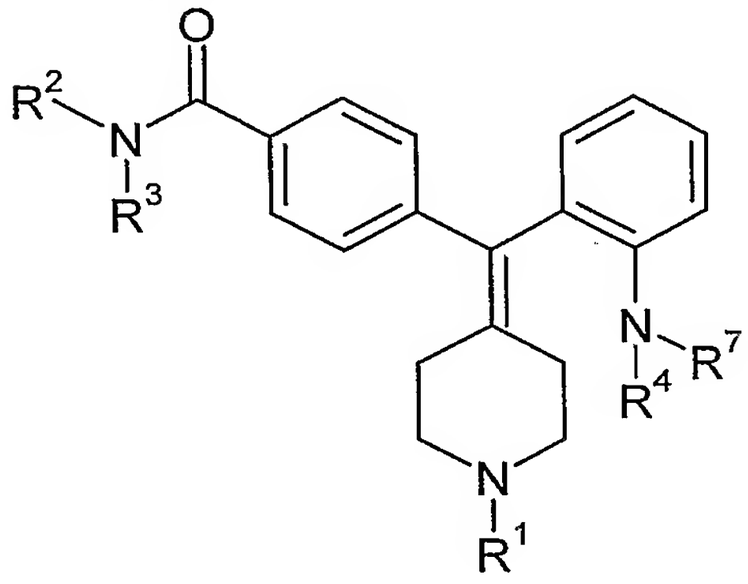
R^2 and R^3 are ethyl;

R^4 is selected from hydrogen and methyl;

R^7 is selected from –H, phenyl, benzyl or phenethyl, cyclohexyl, cyclohexylmethyl, -C(=O)-NH-R^8, –S(=O)$_2$-R^8, and -C(=O)-R^8, wherein R^8 is selected from 2,2,2-trifluoroethyl, phenyl, benzyl or phenethyl, cyclohexyl and cyclohexylmethyl; and

n and m are 0.

In another aspect, the invention provides a compound of formula IA, a pharmaceutically acceptable salt thereof, diastereomers thereof, enantiomers thereof, and mixtures thereof:



IA

wherein

R^1 is selected from hydrogen, C_{1-6}alkyl-O-C(=O)-, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{6-10}aryl, C_{2-9}heterocyclyl, C_{6-10}aryl-C_{1-3}alkyl and C_{2-9}heterocyclyl-C_{1-3}alkyl; wherein said C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{6-10}aryl, C_{2-9}heterocyclyl, C_{6-10}aryl-C_{1-3}alkyl and C_{2-9}heterocyclyl-C_{1-3}alkyl are optionally substituted with one or more groups selected from -R, -NO_2, -OR, -Cl, -Br, -I, -F, -CF_3, -C(=O)R, -C(=O)OH, -NH_2, -SH, -NHR, -NR_2, -SR, -SO_3H, -SO_2R, -S(=O)R, -CN, -OH, -C(=O)OR, -C(=O)NR_2, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen or C_{1-6}alkyl;

R^2, R^3 and R^4 are, independently, selected from hydrogen, C_{1-6}alkyl, and C_{3-6}cycloalkyl, wherein said C_{1-6}alkyl and C_{3-6}cycloalkyl are optionally substituted with one or more groups selected from -R, -NO_2, -OR, -Cl, -Br, -I, -F, -CF_3, -C(=O)R, -C(=O)OH, -NH_2, -SH, -NHR, -NR_2, -SR, -SO_3H, -SO_2R, -S(=O)R, -CN, -OH, -C(=O)OR, -C(=O)NR_2, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen or C_{1-6}alkyl; and

R^7 is selected from –H, -OH, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{6-10}aryl, C_{2-9}heterocyclyl, C_{6-10}aryl-C_{1-6}alkyl, C_{2-9}heterocyclyl-C_{1-6}alkyl, -C(=O)-NR^8R^9, -C(=O)-O-R^8, –S(=O)-R^8, –S(=O)$_2$-R^8, -C(=O)-R^8 and -SO_3H, wherein R^8 and R^9 are independently selected from –H, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{6-10}aryl, C_{2-9}heterocyclyl, C_{6-10}aryl-C_{1-6}alkyl, and C_{2-9}heterocyclyl-C_{1-6}alkyl, wherein said C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{6-10}aryl, C_{2-9}heterocyclyl, C_{6-10}aryl-C_{1-6}alkyl, and C_{2-9}heterocyclyl-C_{1-6}alkyl used in defining R^7, R^8 or R^9 are optionally substituted with one or more groups selected from -R, -NO_2, -OR, -Cl, -Br, -I, -F, -CF_3, -C(=O)R, -C(=O)OH, -NH_2, -SH, -NHR, -NR_2, -SR, -SO_3H, -SO_2R, -S(=O)R, -CN, -OH, -C(=O)OR, -C(=O)NR_2, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen or C_{1-6}alkyl.

In one embodiment, the compounds of the present invention are represented by formula IA, wherein R^1 is selected from hydrogen, C_{1-6}alkyl-O-C(=O)-, C_{1-6}alkyl, C_{3-6}cycloalkyl, benzyl and C_{2-5}heteroarylmethyl, wherein said C_{1-6}alkyl,

C_{3-6}cycloalkyl, benzyl and C_{2-5}heteroarylmethyl are optionally substituted with one or more groups selected from C_{1-6}alkyl, halogenated C_{1-6}alkyl, -CF_3, C_{1-6} alkoxy, chloro, fluoro, bromo, and iodo;

R^2 and R^3 are ethyl;

R^4 is selected from hydrogen and C_{1-3}alkyl;

R^7 is selected from –H, -OH, phenyl, C_{3-5}heterocyclyl, phenyl-C_{1-3}alkyl, C_{3-5}heterocyclyl-C_{1-3}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl-C_{1-3}alkyl, -C(=O)-N-R^8R^9, –C(=O)-O-R^8, –S(=O)-R^8, –S(=O)$_2$-R^8, -C(=O)-R^8 and -SO_3H, wherein R^8 and R^9 are independently selected from –H, phenyl, C_{3-5}heterocyclyl, phenyl-C_{1-3}alkyl, C_{3-5}heterocyclyl-C_{1-3}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl-C_{1-3}alkyl, wherein said phenyl, C_{3-5}heterocyclyl, phenyl-C_{1-3}alkyl, C_{3-5}heterocyclyl-C_{1-3}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl-C_{1-3}alkyl used in defining R^7, R^8 and R^9 are optionally substituted with one or more groups selected from C_{1-6}alkyl, halogenated C_{1-6}alkyl, -CF_3, C_{1-6} alkoxy, chloro, fluoro, bromo, and iodo.

In another embodiment, the compounds of the present invention are represented by formula IA, wherein R^1 is selected from hydrogen, C_{1-6}alkyl-O-C(=O)-, C_{1-6}alkyl, C_{3-6}cycloalkyl, benzyl, thiadiazolylmethyl, pyridylmethyl, thienylmethyl, furylmethyl, imidazolylmethyl, triazolylmethyl, pyrrolylmethyl, thiazolylmethyl and N-oxido-pyridylmethyl, wherein said C_{1-6}alkyl, C_{3-6}cycloalkyl, benzyl, thiadiazolylmethyl, pyridylmethyl, thienylmethyl, furylmethyl, imidazolylmethyl, triazolylmethyl, pyrrolylmethyl, thiazolylmethyl and N-oxido-pyridylmethyl are optionally substituted with one or more groups selected from C_{1-6}alkyl, halogenated C_{1-6}alkyl, -CF_3, C_{1-6} alkoxy, chloro, fluoro, bromo, and iodo;

R^2 and R^3 are ethyl;

R^4 is selected from hydrogen and methyl;

R^7 is selected from –H, C_{1-6}alkyl, phenyl-C_{1-3}alkyl, C_{3-7}cycloalkyl-C_{1-3}alkyl, C_{3-7}cycloalkyl, phenyl, C_{1-6}alkyl, -C(=O)-N-R^8R^9, –S(=O)$_2$-R^8, -C(=O)-O-R^8, and -C(=O)-R^8, wherein R^8 and R^9 are independantly selected from –H, phenyl-C_{1-3}alkyl, C_{3-7}cycloalkyl-C_{1-3}alkyl, C_{3-7}cycloalkyl, phenyl, and C_{1-6}alkyl, wherein said phenyl-

C_{1-3}alkyl, C_{3-7}cycloalkyl-C_{1-3}alkyl, C_{3-7}cycloalkyl, phenyl, C_{1-6}alkyl used in defining R^7, R^8 and R^9 are optionally substituted with one or more groups selected from C_{1-6}alkyl, halogenated C_{1-6}alkyl, -CF_3, C_{1-6} alkoxy, chloro, fluoro, bromo, and iodo.

In a further embodiment, the compounds of the present invention are represented by formula IA, wherein R^1 is selected from hydrogen, propyl, benzyl, thiadiazolylmethyl, pyridylmethyl, thienylmethyl, furylmethyl, imidazolylmethyl, triazolylmethyl, pyrrolylmethyl, thiazolylmethyl and N-oxido-pyridylmethyl;

R^2 and R^3 are ethyl;

R^4 is selected from hydrogen and methyl;

R^7 is selected from –H, ethyl, phenyl, benzyl or phenethyl, napthyl, fluorophenyl, chlorophenyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, cyclohexylmethyl, -C(=O)-NH-R^8, –S(=O)$_2$-R^8, -C(=O)-O-R^8, and -C(=O)-R^8, wherein R^8 is selected from methyl, 2,2,2-trifluoroethyl, phenyl, benzyl, phenethyl, methylphenyl, fluorophenyl, butyl, cyclohexyl and cyclohexylmethyl.

It will be understood that when compounds of the present invention contain one or more chiral centers, the compounds of the invention may exist in, and be isolated as, enantiomeric or diastereomeric forms, or as a racemic mixture. The present invention includes any possible enantiomers, diastereomers, racemates or mixtures thereof, of a compound of Formula I or IA. The optically active forms of the compound of the invention may be prepared, for example, by chiral chromatographic separation of a racemate, by synthesis from optically active starting materials or by asymmetric synthesis based on the procedures described thereafter.

It will also be appreciated that certain compounds of the present invention may exist as geometrical isomers, for example E and Z isomers of alkenes. The present invention includes any geometrical isomer of a compound of Formula I or IA. It will further be understood that the present invention encompasses tautomers of the compounds of the formula I or IA.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It will further be

understood that the present invention encompasses all such solvated forms of the compounds of the formula I or IA.

Within the scope of the invention are also salts of the compounds of the formula I or IA. Generally, pharmaceutically acceptable salts of compounds of the present invention may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound, for example an alkyl amine with a suitable acid, for example, HCl or acetic acid, to afford a physiologically acceptable anion. It may also be possible to make a corresponding alkali metal (such as sodium, potassium, or lithium) or an alkaline earth metal (such as a calcium) salt by treating a compound of the present invention having a suitably acidic proton, such as a carboxylic acid or a phenol with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (such as the ethoxide or methoxide), or a suitably basic organic amine (such as choline or meglumine) in an aqueous medium, followed by conventional purification techniques.

In one embodiment, the compound of formula I or IA above may be converted to a pharmaceutically acceptable salt or solvate thereof, particularly, an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, methanesulphonate or *p*-toluenesulphonate.

The novel compounds of the present invention are useful in therapy, especially for the treatment of various pain conditions such as chronic pain, neuropathic pain, acute pain, cancer pain, pain caused by rheumatoid arthritis, migraine, visceral pain etc. This list should however not be interpreted as exhaustive.

Compounds of the invention are useful as immunomodulators, especially for autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar surgical needs, for collagen diseases, various allergies, for use as anti-tumour agents and anti-viral agents.

Compounds of the invention are useful in disease states where degeneration or dysfunction of opioid receptors is present or implicated in that paradigm. This may involve the use of isotopically labelled versions of the compounds of the invention in

diagnostic techniques and imaging applications such as positron emission tomography (PET).

Compounds of the invention are useful for the treatment of diarrhoea, depression, anxiety and stress-related disorders such as post-traumatic stress disorders, panic disorder, generalized anxiety disorder, social phobia, and obsessive compulsive disorder, urinary incontinence, premature ejaculation, various mental illnesses, cough, lung oedema, various gastro-intestinal disorders, e.g. constipation, functional gastrointestinal disorders such as Irritable Bowel Syndrome and Functional Dyspepsia, Parkinson´s disease and other motor disorders, traumatic brain injury, stroke, cardioprotection following miocardial infarction, spinal injury and drug addiction, including the treatment of alcohol, nicotine, opioid and other drug abuse and for disorders of the sympathetic nervous system for example hypertension.

Compounds of the invention are useful as an analgesic agent for use during general anaesthesia and monitored anaesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain the anaesthetic state (e.g. amnesia, analgesia, muscle relaxation and sedation). Included in this combination are inhaled anaesthetics, hypnotics, anxiolytics, neuromuscular blockers and opioids.

Also within the scope of the invention is the use of any of the compounds according to the formula I or IA above, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

A further aspect of the invention is a method for the treatment of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the formula I or IA above, is administered to a patient in need of such treatment.

Thus, the invention provides a compound of formula I or IA, or pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula I or IA, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The term "therapeutic" and "therapeutically" should be contrued accordingly. The term "therapy" within the context of the present invention further encompasses to administer an effective amount of a compound of the present invention, to mitigate either a pre-existing disease state, acute or chronic, or a recurring condition. This definition also encompasses prophylactic therapies for prevention of recurring conditions and continued therapy for chronic disorders.

The compounds of the present invention are useful in therapy, especially for the therapy of various pain conditions including, but not limited to: chronic pain, neuropathic pain, acute pain, back pain, cancer pain, and visceral pain.

In use for therapy in a warm-blooded animal such as a human, the compound of the invention may be administered in the form of a conventional pharmaceutical composition by any route including orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

In one embodiment of the invention, the route of administration may be orally, intravenously or intramuscularly.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level at the most appropriate for a particular patient.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid and liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or table disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided compound of the invention, or the active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture in then poured into convenient sized moulds and allowed to cool and solidify.

Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term composition is also intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form compositions include solutions, suspensions, and emulsions. For example, sterile water or water propylene glycol solutions of the active compounds may be liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous

material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Depending on the mode of administration, the pharmaceutical composition will preferably include from 0.05% to 99%w (per cent by weight), more preferably from 0.10 to 50%w, of the compound of the invention, all percentages by weight being based on total composition.

A therapeutically effective amount for the practice of the present invention may be determined, by the use of known criteria including the age, weight and response of the individual patient, and interpreted within the context of the disease which is being treated or which is being prevented, by one of ordinary skills in the art.

Within the scope of the invention is the use of any compound of formula I or IA as defined above for the manufacture of a medicament.

Also within the scope of the invention is the use of any compound of formula I or IA for the manufacture of a medicament for the therapy of pain.

Additionally provided is the use of any compound according to Formula I or IA for the manufacture of a medicament for the therapy of various pain conditions including, but not limited to: chronic pain, neuropathic pain, acute pain, back pain, cancer pain, and visceral pain.

A further aspect of the invention is a method for therapy of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the formula I or IA above, is administered to a patient in need of such therapy.

Additionally, there is provided a pharmaceutical composition comprising a compound of Formula I or IA, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

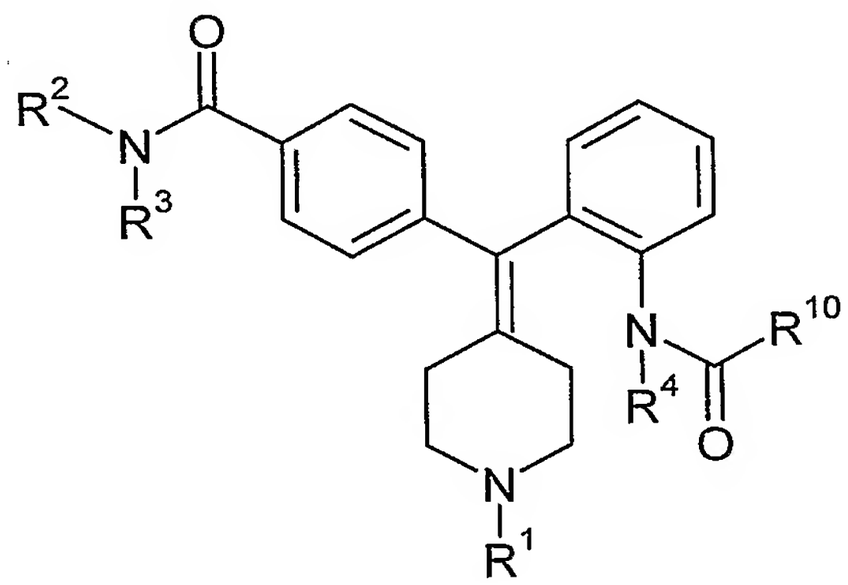
Particularly, there is provided a pharmaceutical composition comprising a compound of Formula I or IA, or a pharmaceutically acceptable salt thereof, in

association with a pharmaceutically acceptable carrier for therapy, more particularly for therapy of pain.

Further, there is provided a pharmaceutical composition comprising a compound of Formula I or IA, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier use in any of the conditions discussed above.

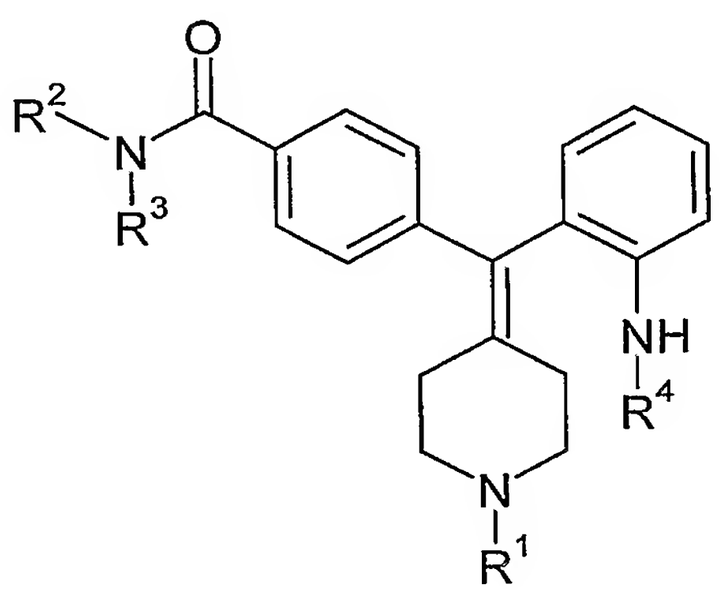
In a further aspect, the present invention provides a method of preparing a compound of formula I or IA.

In one embodiment, the invention provides a process for preparing a compound of formula II, comprising:



II

reacting a compound of formula III with X^1-C(=O)-R^{10}:



,

III

wherein

R^1 is selected from C_{1-6}alkyl-O-C(=O)-, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl and optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl;

X^1 is selected from –OH, -OR^{11}, -O-C(=O)-R^{11}, -Cl, -Br and -I, wherein R^{11} is C_{1-6}alkyl;

R^2, R^3 and R^4 are, independently, selected from hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-6}cycloalkyl; and

R^{10} is selected from –H, optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl, optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl and optionally substituted C_{3-6}cycloalkyl-C_{1-3}alkyl.

Particularly, the invention provides a process for preparing a compound of formula II as described above, wherein

R^1 is C_{1-6}alkyl-O-C(=O)-;

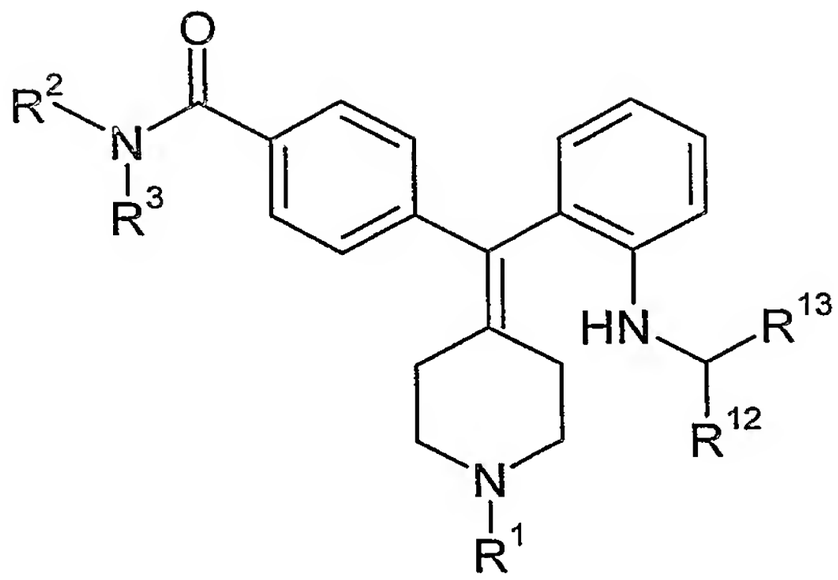
X^1 is selected from –OH, -Cl, -Br and -I;

R^2 and R^3 are ethyl;

R^4 is hydrogen; and

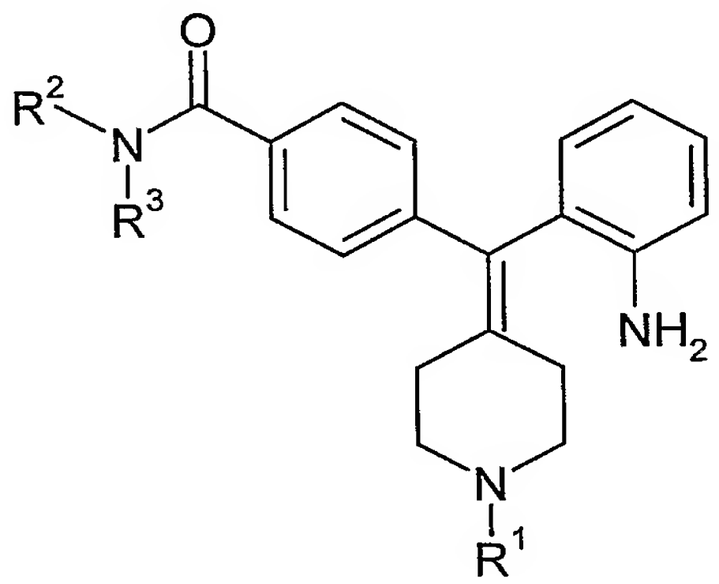
R^{10} is selected from phenyl, phenyl-C_{1-3}alkyl, C_{1-6}alkyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkyl-C_{1-3}alkyl.

In a second embodiment, the present invention provides a process for preparing a compound of formula IV, comprising:



IV

reacting a compound of formula V with R^{12}-C(=O)-R^{13}:



V

wherein

R^1 is selected from C_{1-6}alkyl-O-C(=O)-, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl and optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl;

R^2 and R^3 are, independently, selected from hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-6}cycloalkyl; and

R^{12} and R^{13} are independently selected from –H, optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl,

optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl and optionally substituted C_{3-6}cycloalkyl-C_{1-3}alkyl; or R^{12} and R^{13} together form a portion of a C_{3-6}cycloalkyl ring or a C_{3-5}heterocylcyl ring.

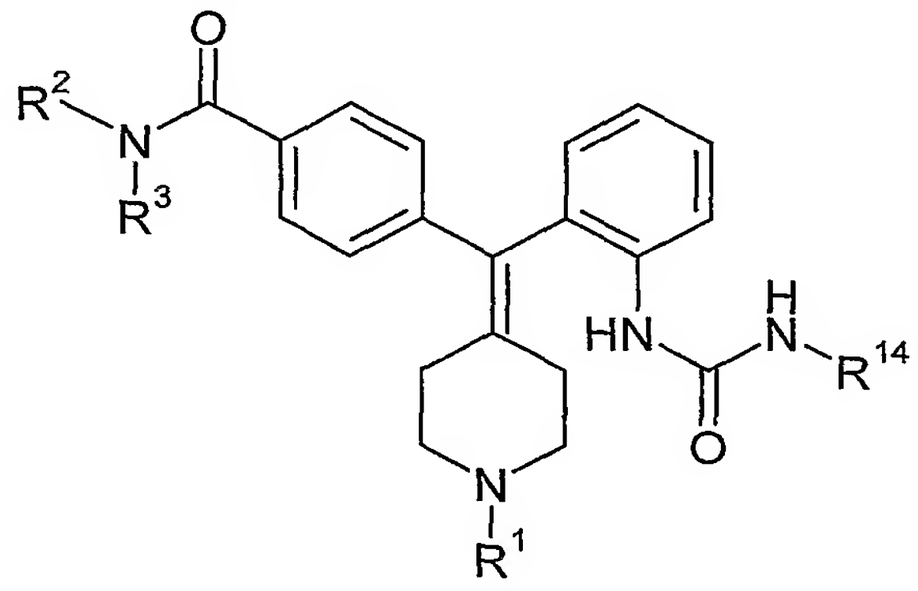
Particularly, the invention provides a process for preparing a compound of formula IV as described above, wherein

R^1 is C_{1-6}alkyl-O-C(=O)-;

R^2 and R^3 are ethyl; and

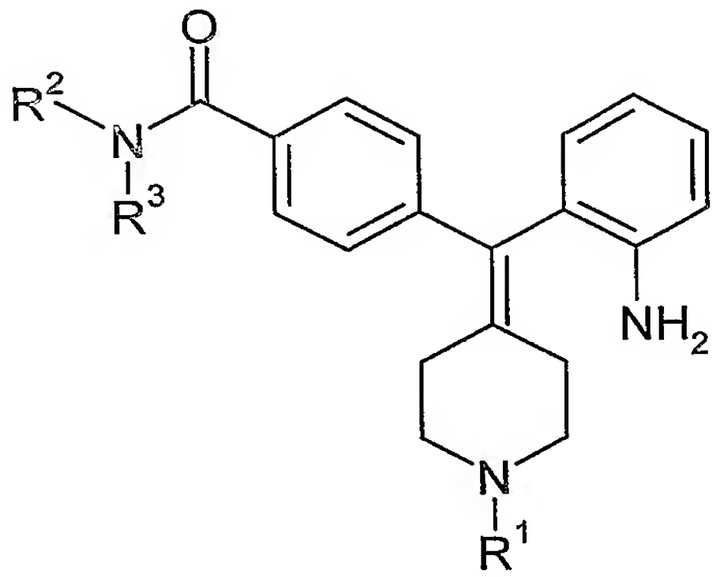
R^{12} and R^{13} are independently selected from –H, phenyl, phenyl-C_{1-3}alkyl, C_{1-6}alkyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkyl-C_{1-3}alkyl; or R^{12} and R^{13} together form a portion of a C_{3-6}cycloalkyl ring.

In a third embodiment, the present invention provides a process for preparing a compound of formula VI, comprising:



VI

reacting a compound of formula V with R^{14}-NCO:



V

wherein

R^1 is C_{1-6}alkyl-O-C(=O)-, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl or optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl;

R^2 and R^3 are, independently, selected from hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-6}cycloalkyl; and

R^{14} is selected from optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl, optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl and optionally substituted C_{3-6}cycloalkyl-C_{1-3}alkyl.

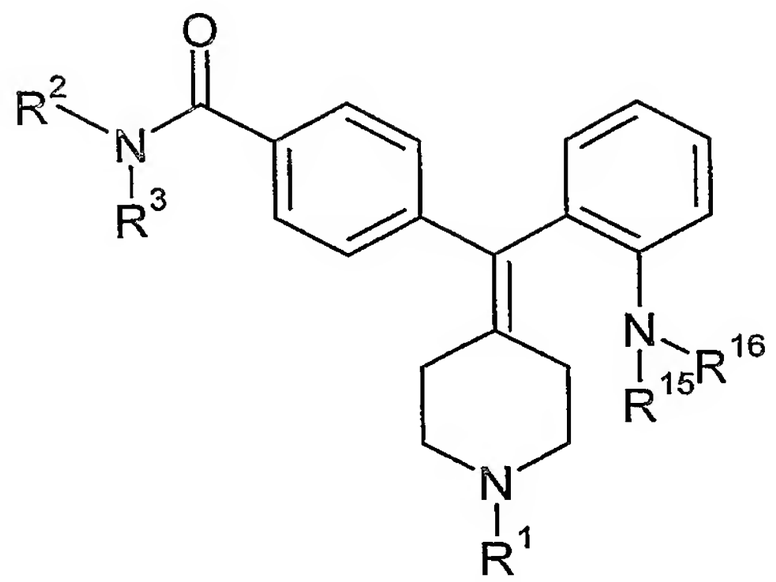
Particularly, the invention provides a process for preparing a compound of formula VI as described above, wherein

R^1 is C_{1-6}alkyl-O-C(=O)-;

R^2 and R^3 are ethyl; and

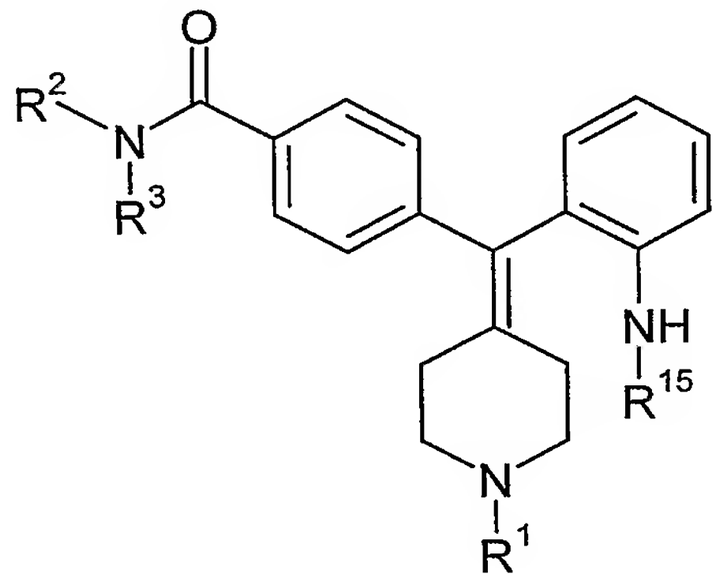
R^{14} is selected from phenyl, phenyl-C_{1-3}alkyl, C_{1-6}alkyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkyl-C_{1-3}alkyl.

In a fourth embodiment, the present invention provides a process for preparing a compound of formula VII, comprising:



VII

reacting a compound of formula VIII with R^{16}-X^2:



VIII

wherein

R^1 is selected from C_{1-6}alkyl-O-C(=O)-, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl and optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl;

R^2 and R^3 are, independently, selected from hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-6}cycloalkyl;

X^2 is selected from I, Br and Cl;

R^{15} is selected from –H, optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl, optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl and optionally substituted C_{3-6}cycloalkyl-C_{1-3}alkyl; and

R^{16} is selected from optionally substituted phenyl-C_{1-3}alkyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl and optionally substituted C_{3-6}cycloalkyl-C_{1-3}alkyl.

Particularly, the invention provides a process for preparing a compound of formula VII as described above, wherein

R^1 is C_{1-6}alkyl-O-C(=O)-;

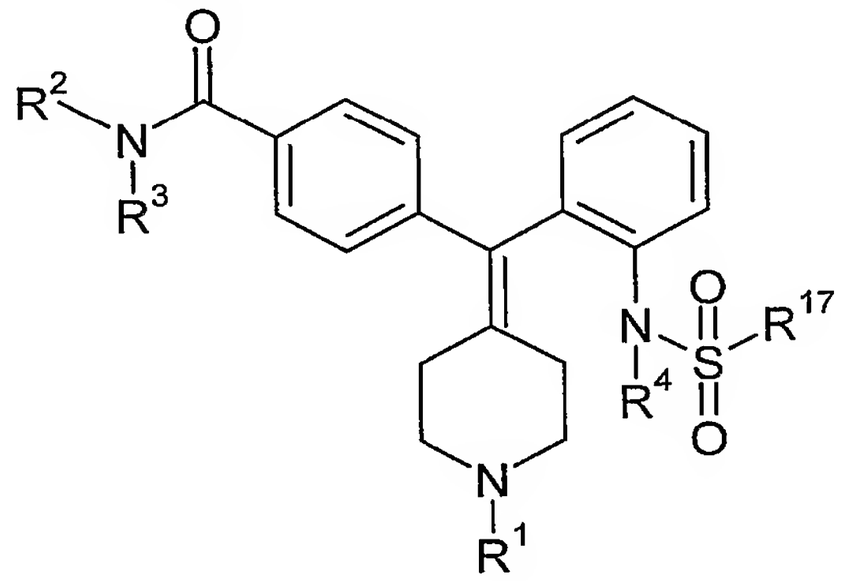
X^2 is selected from -Cl, -Br and -I;

R^2 and R^3 are ethyl;

R^{15} is selected from hydrogen and methyl; and

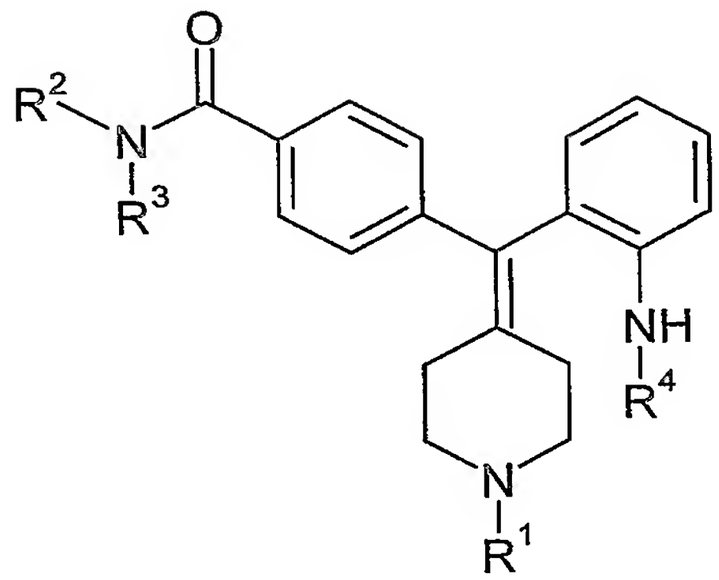
R^{16} is selected from phenyl, phenyl-C_{1-3}alkyl, C_{1-6}alkyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkyl-C_{1-3}alkyl.

In a fifth embodiment, the present invention provides a process for preparing a compound of formula IX, comprising:



IX

reacting a compound of formula III with X^3-S(=O)$_2$-R^{17}:



III

wherein

R^1 is selected from C_{1-6}alkyl-O-C(=O)-, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl and optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl;

X^3 is selected from –OH, -OR^{11}, -Cl, -Br and -I, wherein R^{11} is C_{1-6}alkyl;

R^2, R^3 and R^4 are, independently, selected from hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-6}cycloalkyl; and

R^{17} is selected from –H, optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl, optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl and optionally substituted C_{3-6}cycloalkyl-C_{1-3}alkyl.

Particularly, the invention provides a process for preparing a compound of formula IX as described above, wherein

R^1 is C_{1-6}alkyl-O-C(=O)-;

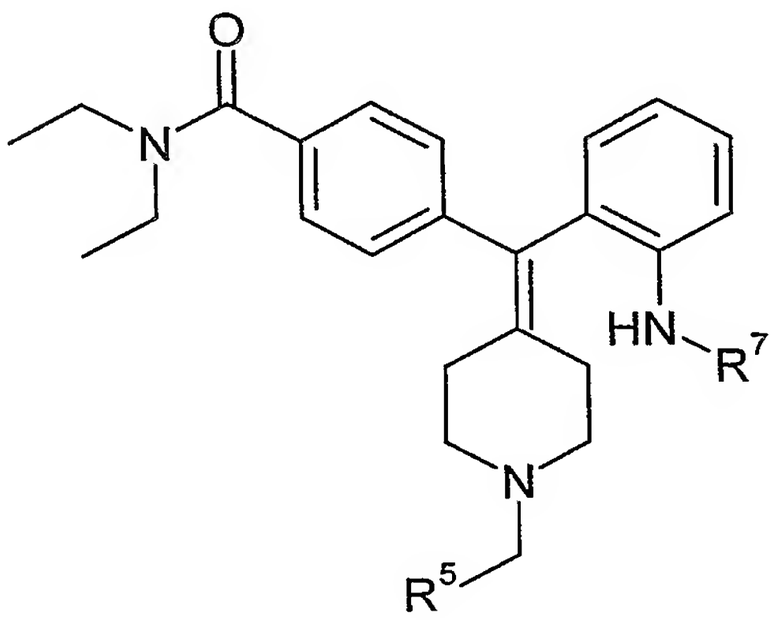
X^3 is selected from -Cl, -Br and -I;

R^2 and R^3 are ethyl;

R^4 is hydrogen;

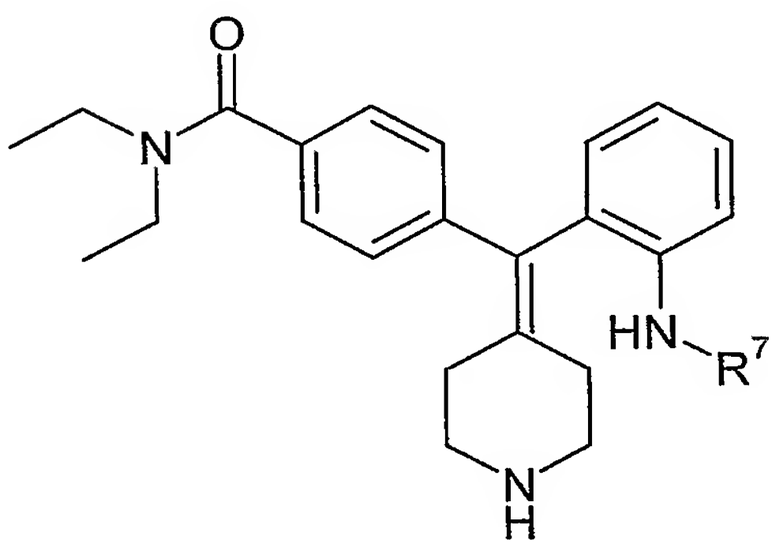
R^{17} is selected from phenyl, phenyl-C_{1-3}alkyl, optionally substituted C_{1-6}alkyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkyl-C_{1-3}alkyl.

In another embodiment, the present invention provides a process for preparing a compound of formula IIA, comprising:



IIA

reacting a compound of formula IIIA with R^5-CH_2-X or R^5-CHO:



IIIA

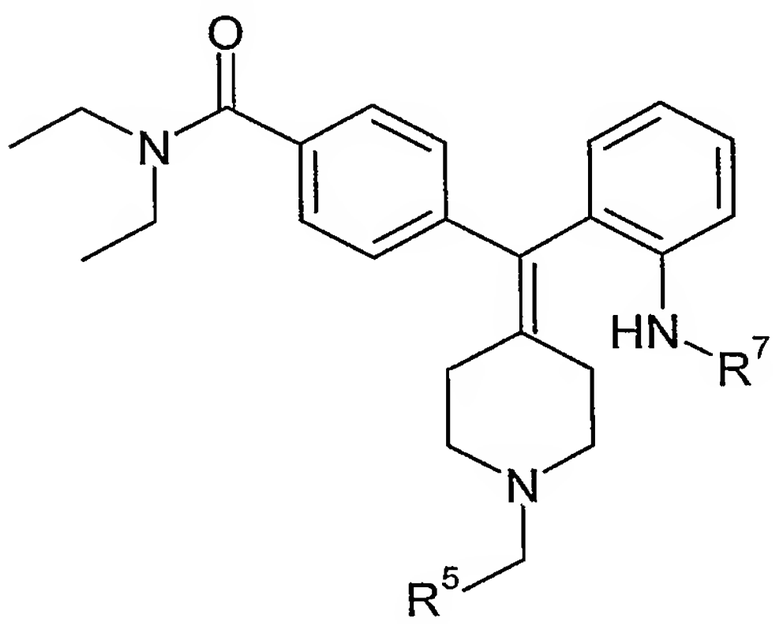
wherein X is a halogen;

R^7 is selected from –C(=O)-O-R^8, –S(=O)-R^8, –S(=O)$_2$-R^8, and -C(=O)-R^8, wherein R^8 is selected from C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{6-10}aryl, C_{2-9}heterocyclyl, C_{6-10}aryl-C_{1-6}alkyl, and C_{2-9}heterocyclyl-C_{1-6}alkyl, wherein said C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{6-10}aryl, C_{2-9}heterocyclyl, C_{6-10}aryl-C_{1-6}alkyl, and C_{2-9}heterocyclyl-C_{1-6}alkyl are optionally substituted with one or more groups selected from -R, -NO_2,

-OR, -Cl, -Br, -I, -F, $-CF_3$, -C(=O)R, -C(=O)OH, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $-SO_3H$, $-SO_2R$, -S(=O)R, -CN, -OH, -C(=O)OR, $-C(=O)NR_2$, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen or C_{1-6}alkyl; and

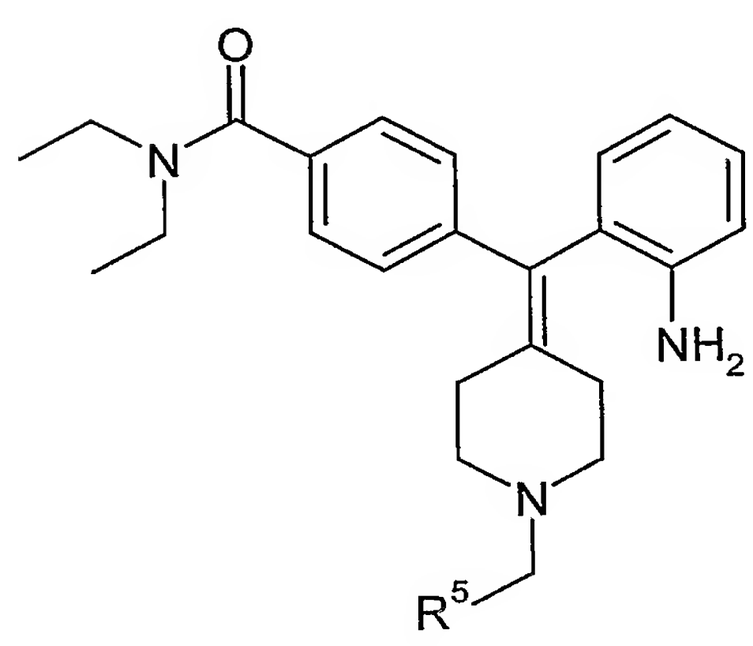
R^5 is selected from C_{6-10}aryl and C_{2-5}heteroaryl, wherein said C_{6-10}aryl and C_{2-5}heteroaryl are optionally substituted with one or more groups selected from -R, $-NO_2$, -OR, -Cl, -Br, -I, -F, $-CF_3$, -C(=O)R, -C(=O)OH, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $-SO_3H$, $-SO_2R$, -S(=O)R, -CN, -OH, -C(=O)OR, $-C(=O)NR_2$, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen or C_{1-6}alkyl.

In another embodiment, the present invention provides a process for preparing a compound of formula IIA, comprising:



IIA

reacting a compound of formula IVA with R^7-X or R^7-O-R^7:



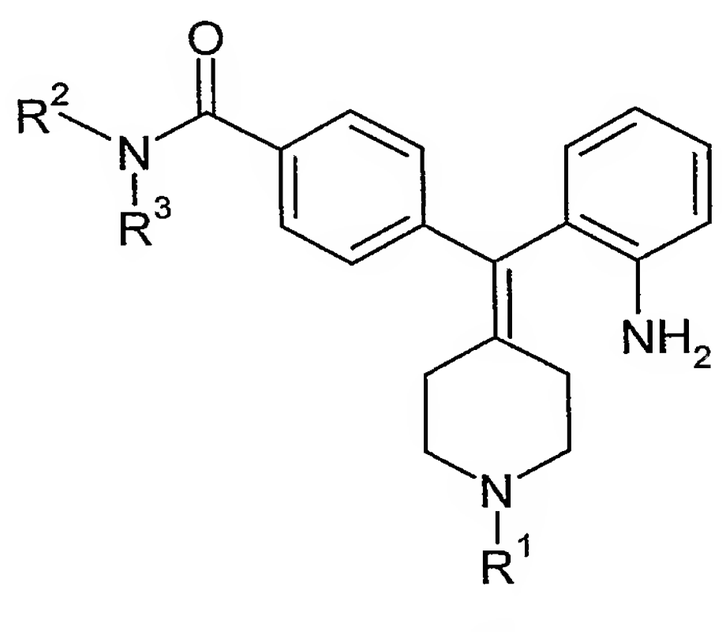
IVA

wherein X is a halogen;

R^7 is selected from –C(=O)-O-R^8 and -C(=O)-R^8, wherein R^8 is selected from C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{6-10}aryl, C_{2-9}heterocyclyl, C_{6-10}aryl-C_{1-6}alkyl, and C_{2-9}heterocyclyl-C_{1-6}alkyl, wherein said C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{6-10}aryl, C_{2-9}heterocyclyl, C_{6-10}aryl-C_{1-6}alkyl, and C_{2-9}heterocyclyl-C_{1-6}alkyl are optionally substituted with one or more groups selected from -R, $-NO_2$, -OR, -Cl, -Br, -I, -F, $-CF_3$, -C(=O)R, -C(=O)OH, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $-SO_3H$, $-SO_2R$, -S(=O)R, -CN, -OH, -C(=O)OR, $-C(=O)NR_2$, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen or C_{1-6}alkyl; and

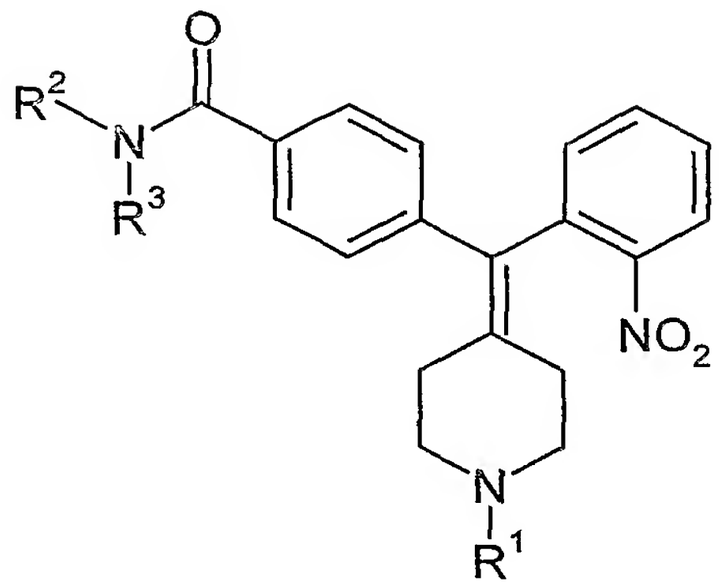
R^5 is selected from C_{6-10}aryl and C_{2-5}heteroaryl, wherein said C_{6-10}aryl and C_{2-5}heteroaryl are optionally substituted with one or more groups selected from -R, $-NO_2$, -OR, -Cl, -Br, -I, -F, $-CF_3$, -C(=O)R, -C(=O)OH, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $-SO_3H$, $-SO_2R$, -S(=O)R, -CN, -OH, -C(=O)OR, $-C(=O)NR_2$, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen or C_{1-6}alkyl.

In a further embodiment, the present invention provides a process of preparing a compound of formula VA,



VA

comprising reducing a compound of formula VIA,



VIA

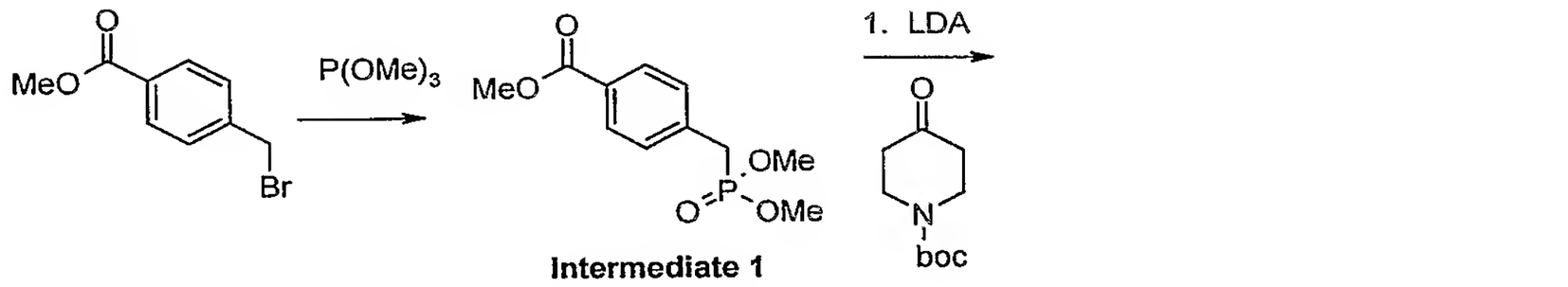
wherein

R^1 is selected from hydrogen, C_{1-6}alkyl-O-C(=O)-, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{6-10}aryl, C_{2-9}heterocyclyl, C_{6-10}aryl-C_{1-3}alkyl and C_{2-9}heterocyclyl-C_{1-3}alkyl; wherein said C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{6-10}aryl, C_{2-9}heterocyclyl, C_{6-10}aryl-C_{1-3}alkyl and C_{2-9}heterocyclyl-C_{1-3}alkyl are optionally substituted with one or more groups selected from -R, -NO_2, -OR, -Cl, -Br, -I, -F, -CF_3, -C(=O)R, -C(=O)OH, -NH_2, -SH, -NHR, -NR_2, -SR, -SO_3H, -SO_2R, -S(=O)R, -CN, -OH, -C(=O)OR, -C(=O)NR_2, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen or C_{1-6}alkyl; and

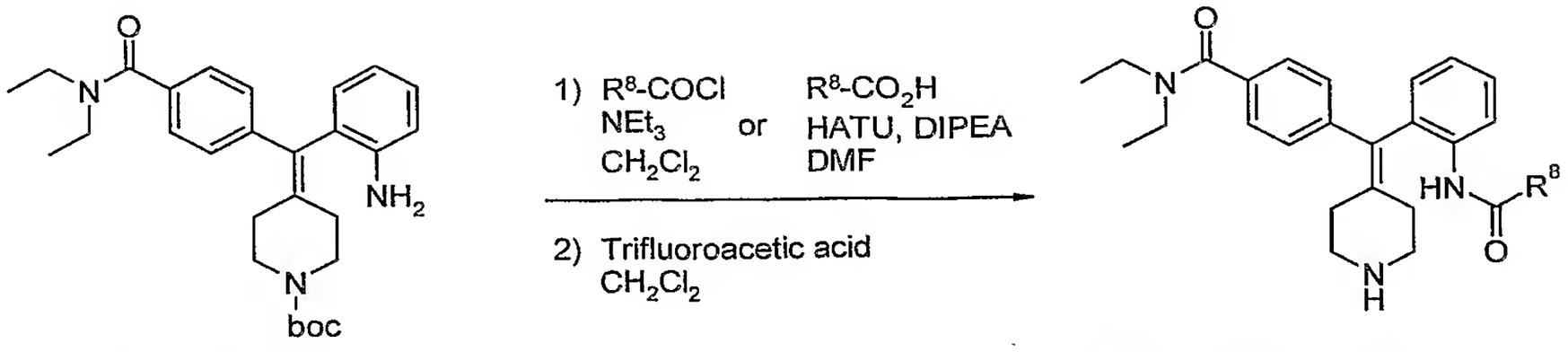
R^2 and R^3 are, independently, selected from hydrogen, C_{1-6}alkyl, and C_{3-6}cycloalkyl, wherein said C_{1-6}alkyl and C_{3-6}cycloalkyl are optionally substituted with one or more groups selected from -R, -NO_2, -OR, -Cl, -Br, -I, -F, -CF_3, -C(=O)R, -C(=O)OH, -NH_2, -SH, -NHR, -NR_2, -SR, -SO_3H, -SO_2R, -S(=O)R, -CN, -OH, -C(=O)OR, -C(=O)NR_2, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen or C_{1-6}alkyl.

Particularly, the compounds of the present invention and intermediates used for the preparation thereof can be prepared according to the synthetic routes as exemplified in Schemes 1-18.

Scheme 1


MeO
O
Br
P(OMe)3
OMe
OMe
1. LDA
N
boc
Intermediate 1
Br2
Br
NaOH
HO
Intermediate 2
Intermediate 3
Intermediate 4
isobutyl chloroformate
Et3N, Et2NH
HO
B
OH
NH2
Pd(PPh3)4, Na2CO3
toluene/EtOH/H2O
Intermediate 5
Intermediate 6

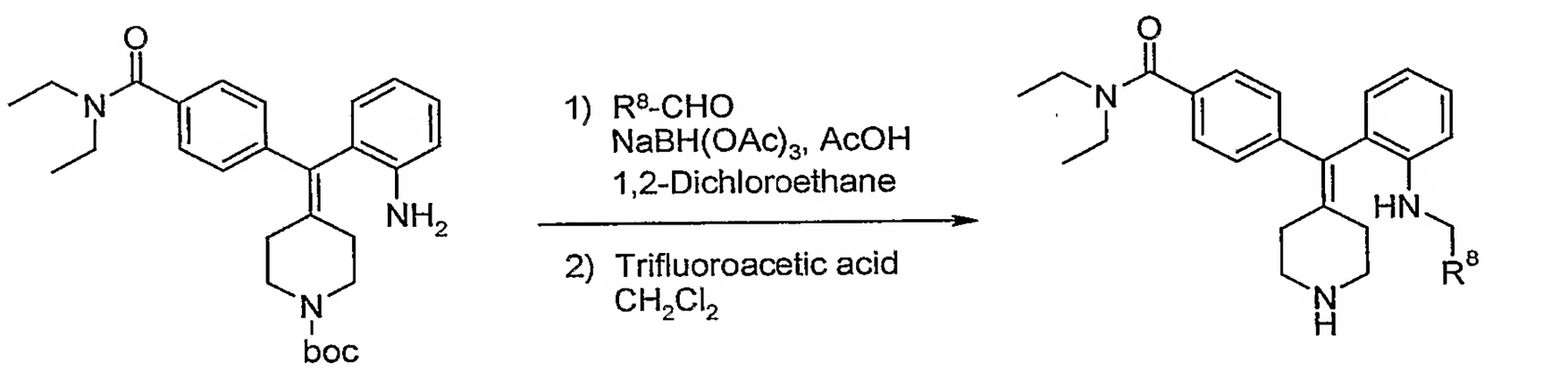
Scheme 2



Intermediate 6

Compound 1: R^8=Ph
Compound 2: R^8=CH_2Ph
Compound 3: R^8=C_6H_{11}
Compound 4: R^8=CH_2CH_2Ph
Compound 5: R^8=$CH_2C_6H_{11}$
Compound 16: R^8=$CH_2C_5H_9$
Compound 17: R^8=C_5H_9

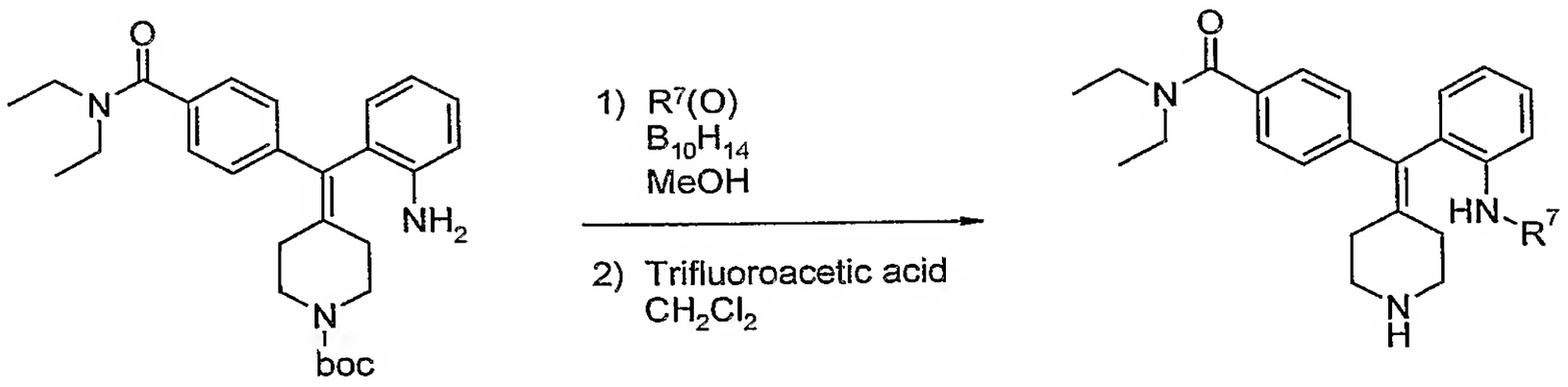
Scheme 3



Intermediate 6

Compound 6: R^8=CH_2Ph
Compound 7: R^8=C_6H_{11}
Compound 8: R^8=Ph
Compound18: R^8=CH_2CH_2Ph
Compound 19: R^8=$CH_2C_6H_{11}$

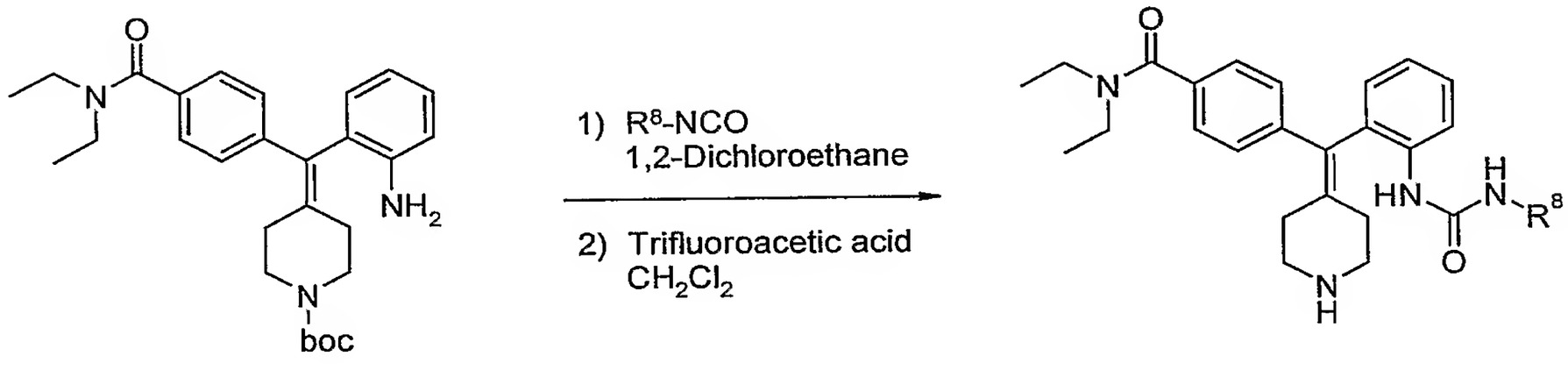
Scheme 4



Intermediate 6

Compound 9: $R^7=C_6H_{11}$
Compound 20: $R^7=C_5H_9$
Compound 21: $R^7=C_7H_{13}$

Scheme 5

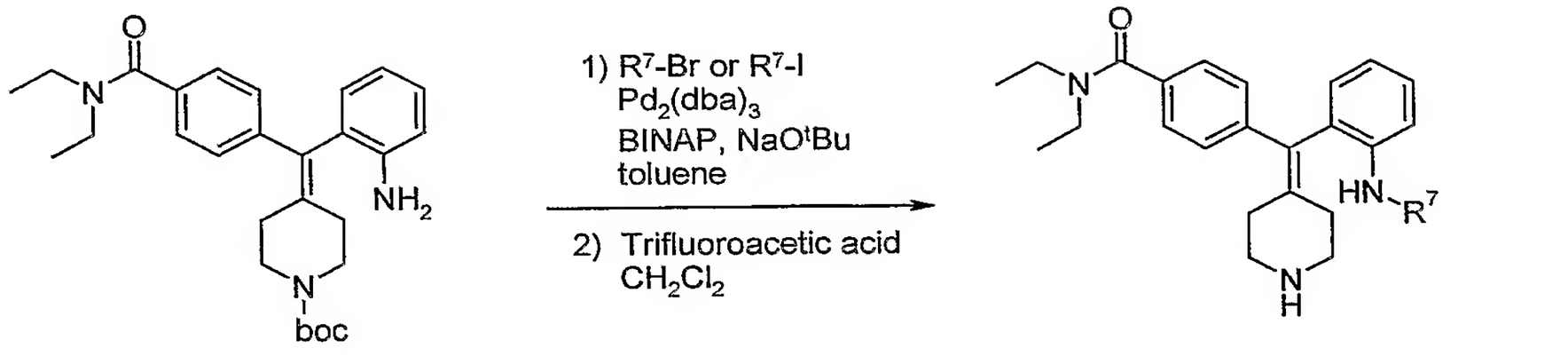


Intermediate 6

Compound 10: R^8=Ph
Compound 22: $R^8=CH_2Ph$

5

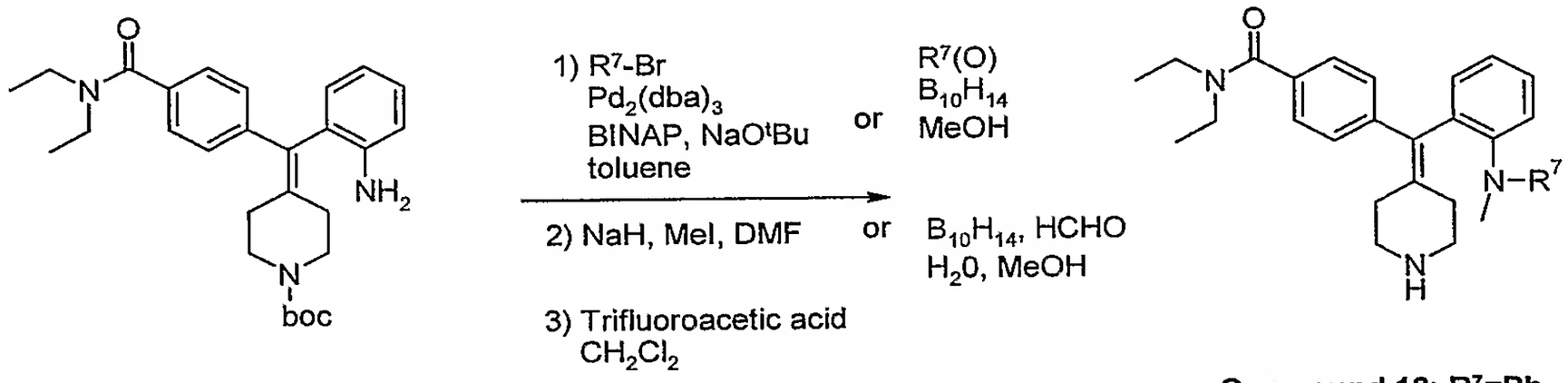
Scheme 6



Intermediate 6

Compound 11: R^7=Ph
Compound 23: R^7=1-Napthyl
Compound 24: R^7=3-F-Ph
Compound 25: R^7=4-Cl-Ph

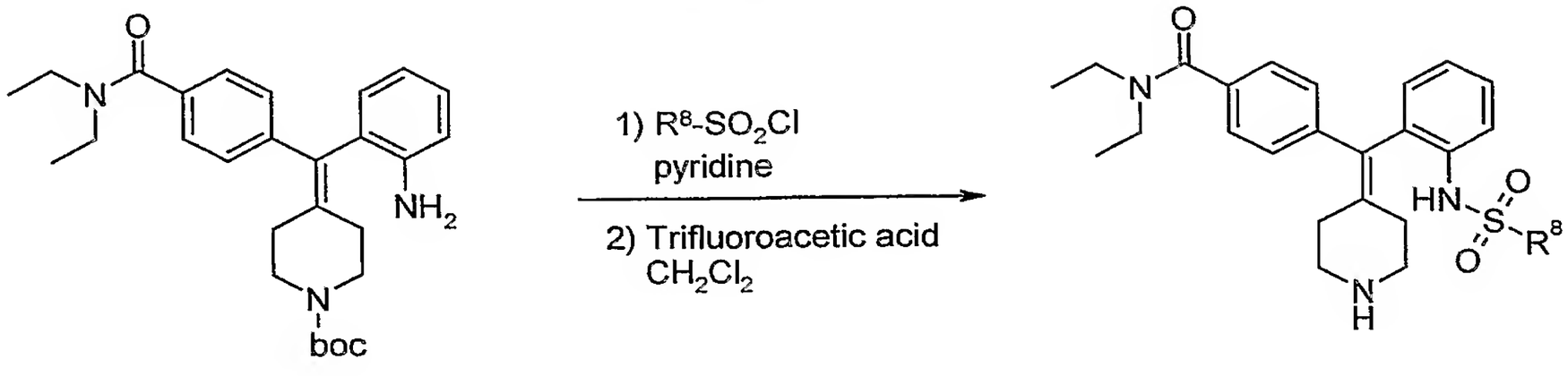
Scheme 7



Intermediate 6

Compound 12: R^7=Ph
Compound 26: R^7=C_6H_{11}

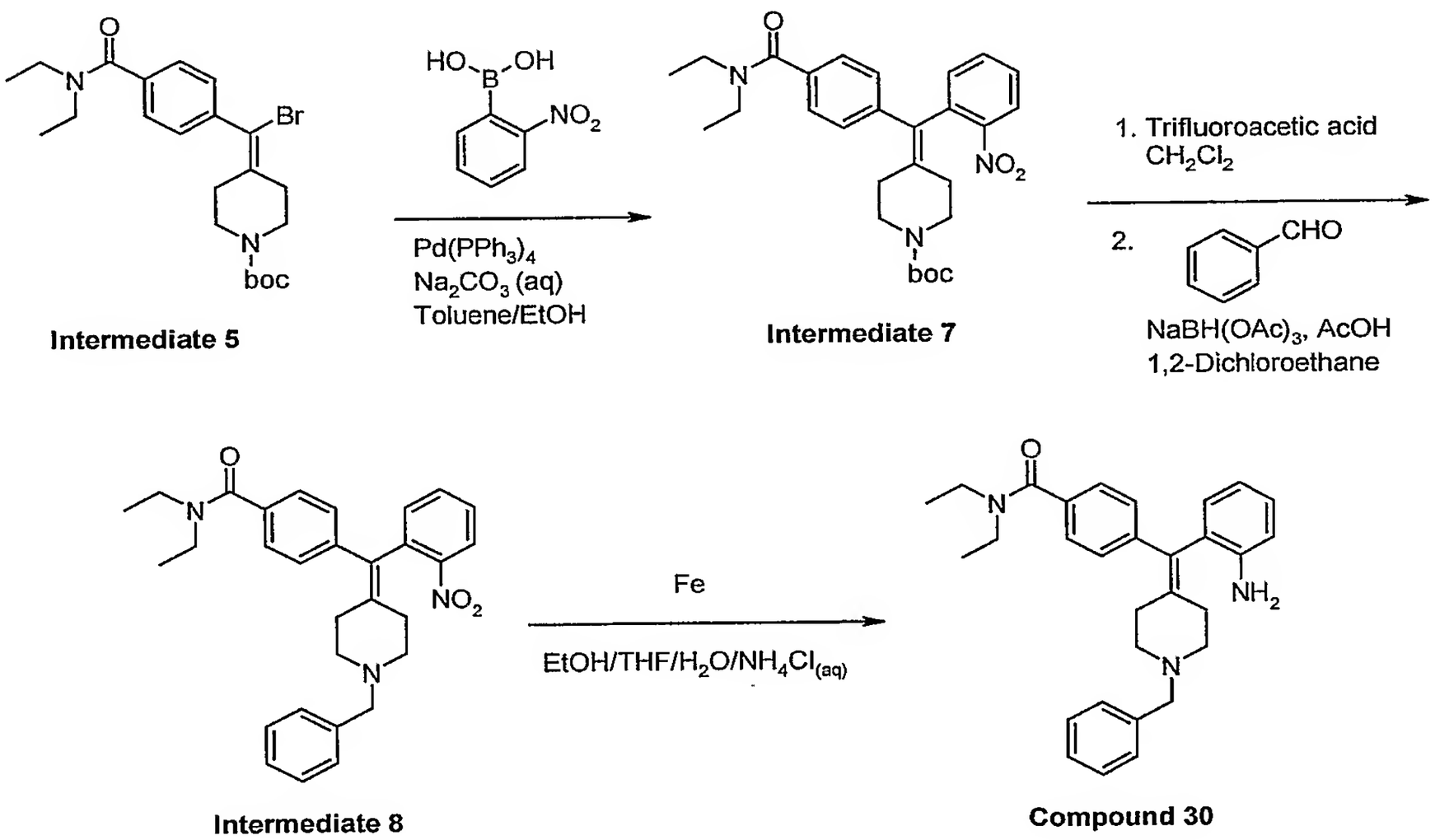
Scheme 8



Intermediate 6

Compound 13: R^8=Ph
Compound 14: R^8=CH_2Ph
Compound 15: R^8=CH_2CF_3
Compound 27: R^8=4-Me-Ph
Compound 28: R^8=2-F-Ph
Compound 29: R^8=n-Bu

Scheme 9



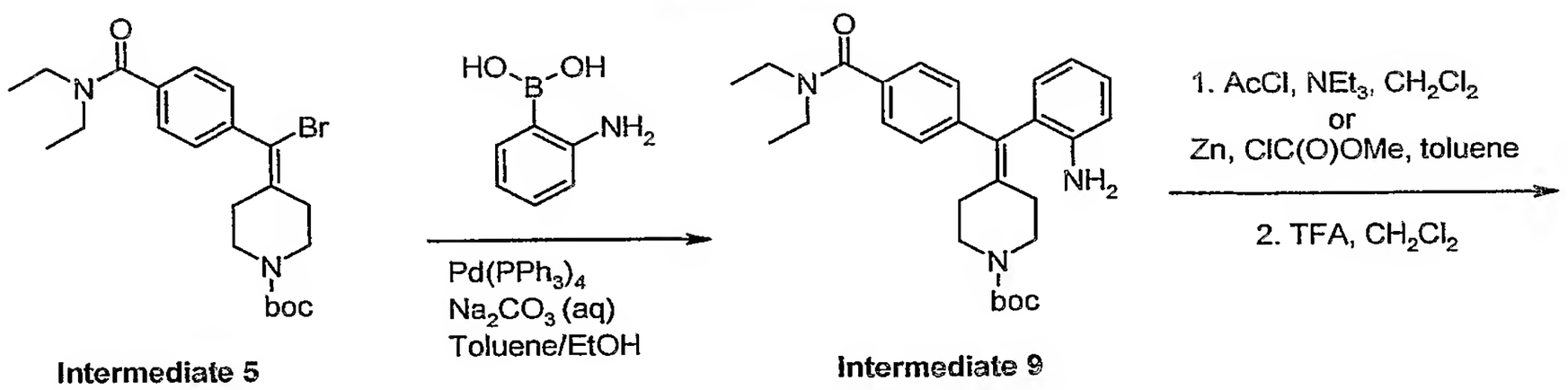
Intermediate 5

Intermediate 7

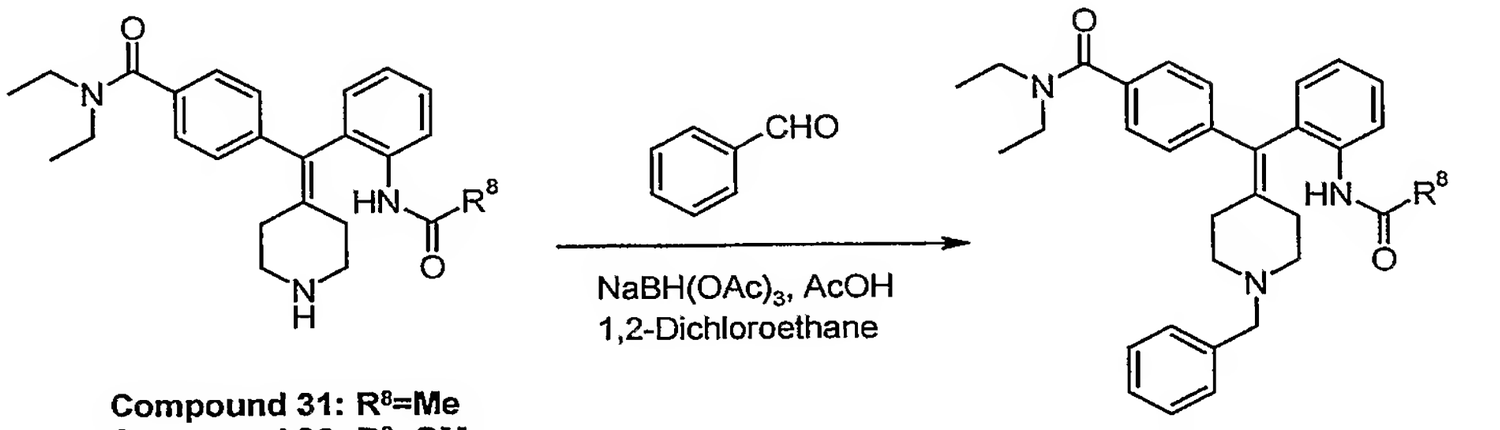
Intermediate 8

Compound 30

Scheme 10



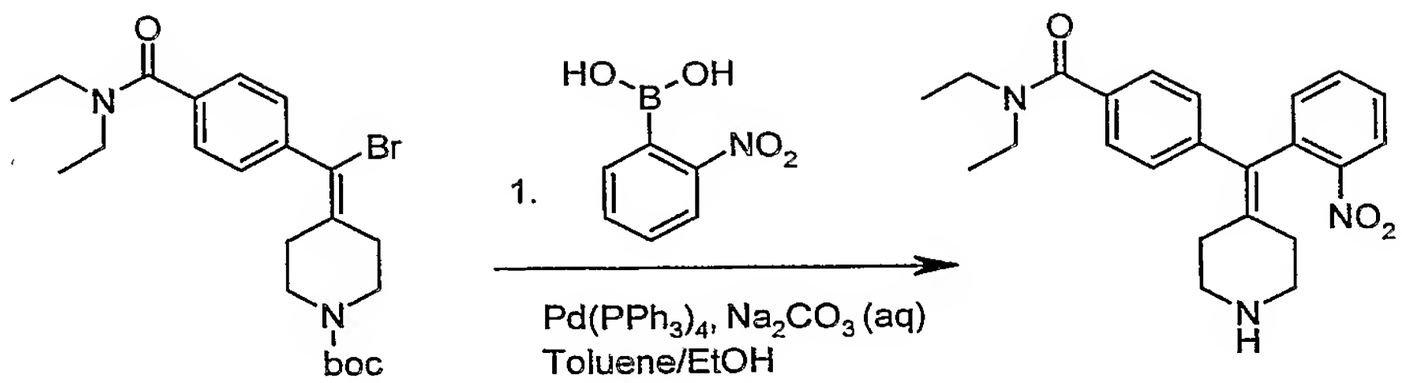
Intermediate 5 **Intermediate 9**



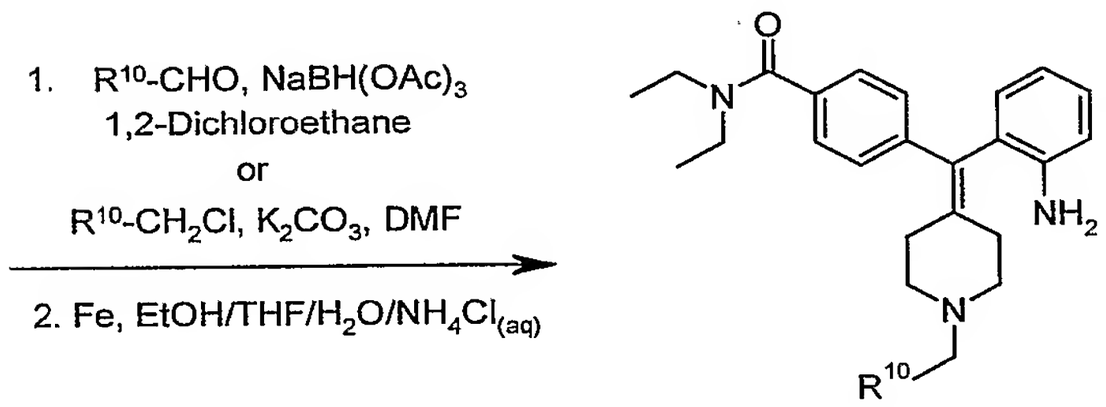
Compound 31: R^8=Me
Compound 32: R^8=OMe

Compound 33: R^8=Me
Compound 34: R^8=OMe

Scheme 11

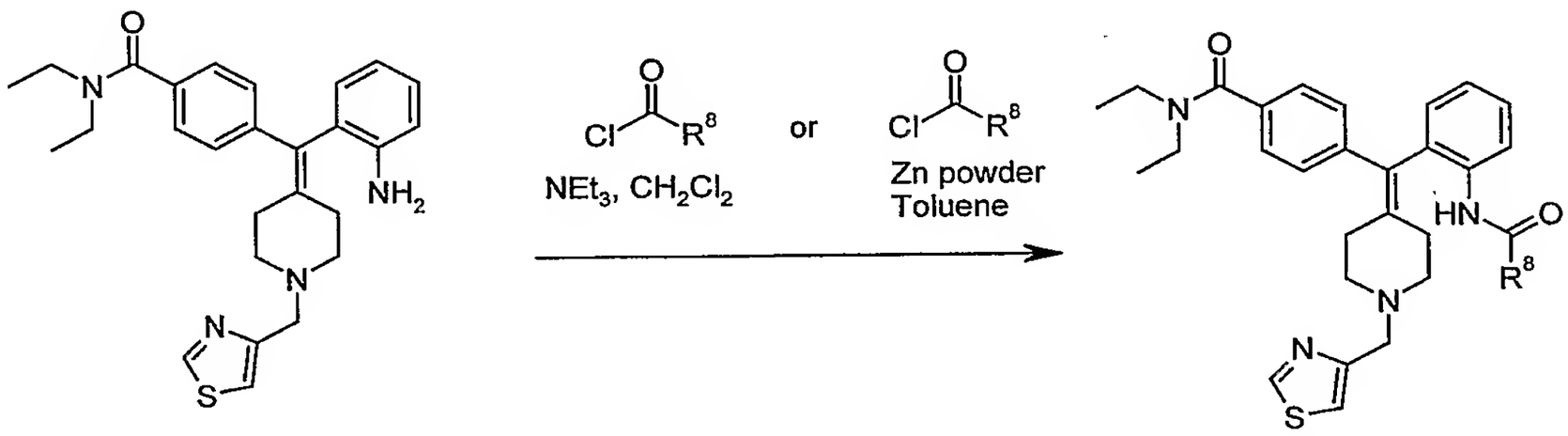


Intermediate 5 **Intermediate 10**



Compound 35: R^{10}=4-thiazolyl
Compound 36: R^{10}=5-thiazolyl

Scheme 12

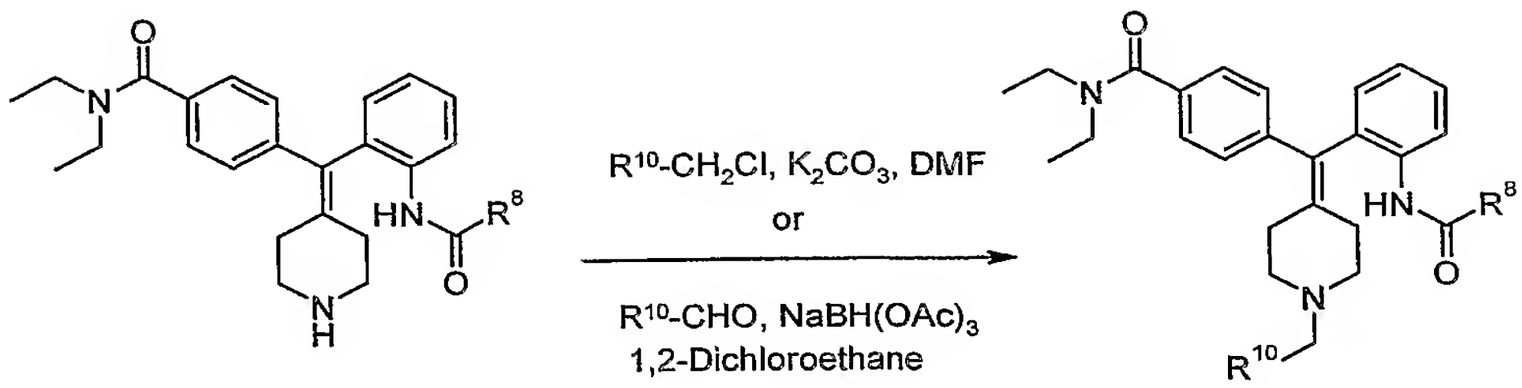


Compound 35

Compound 37: R^8=Me
Compound 38: R^8=OMe

5

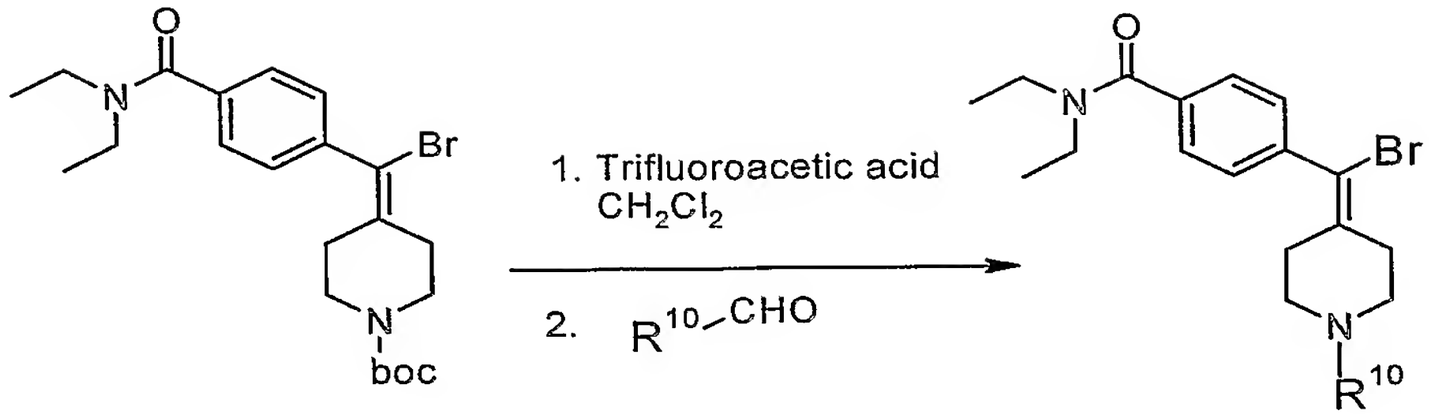
Scheme 13



Compound 31: R^8=Me
Compound 32: R^8=OMe

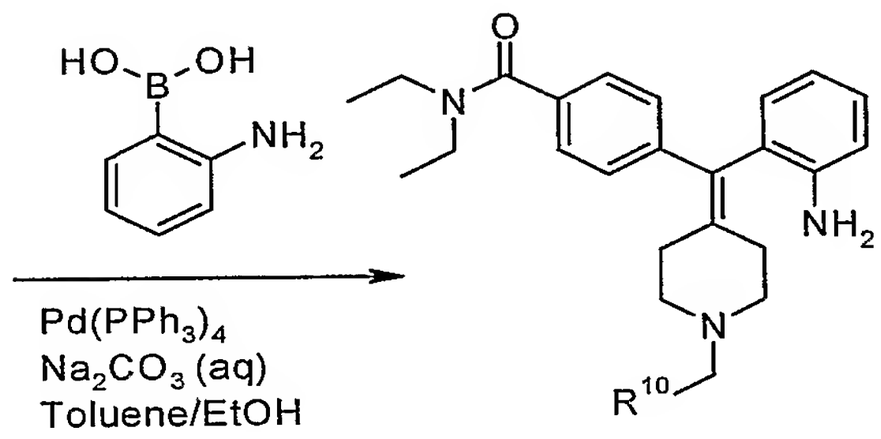
Compound 39: R^8=Me, R^{10}=5-thiazolyl
Compound 40: R^8=OMe, R^{10}=5-thiazolyl

Scheme 14



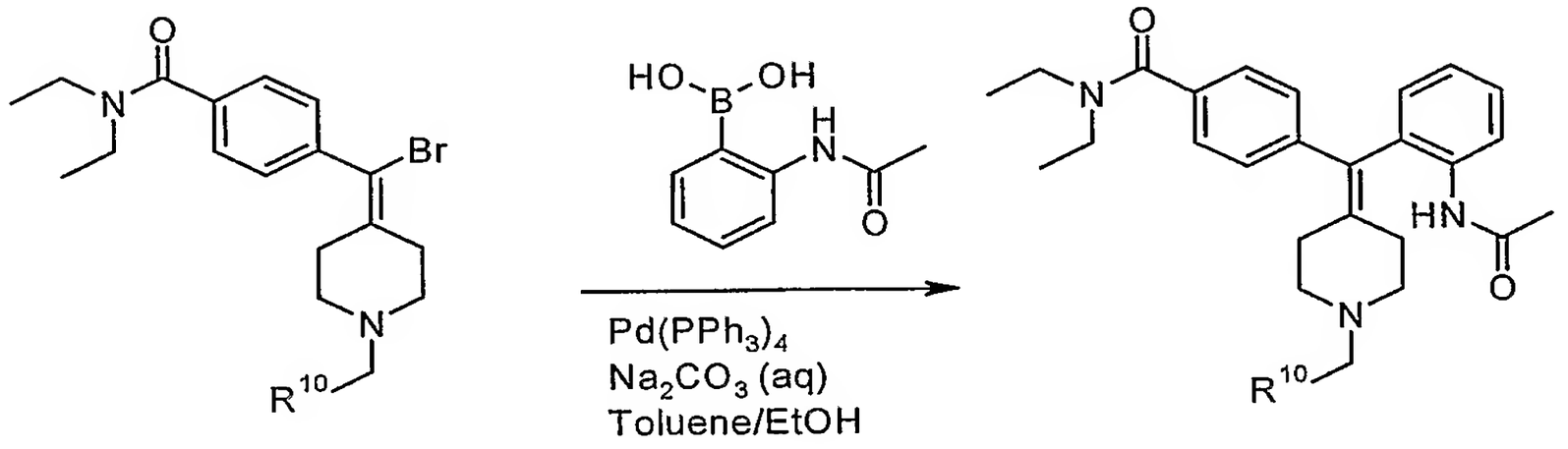
Intermediate 5

Intermediate 11 R^{10}=n-propyl
Intermediate 12 R^{10}=4-pyridyl
Intermediate 13 R^{10}=3-pyridyl
Intermediate 14 R^{10}=2-pyridyl



Compound 41 R^{10}=n-propyl
Compound 42 R^{10}=4-pyridyl
Compound 43 R^{10}=3-pyridyl
Compound 44 R^{10}=2-pyridyl

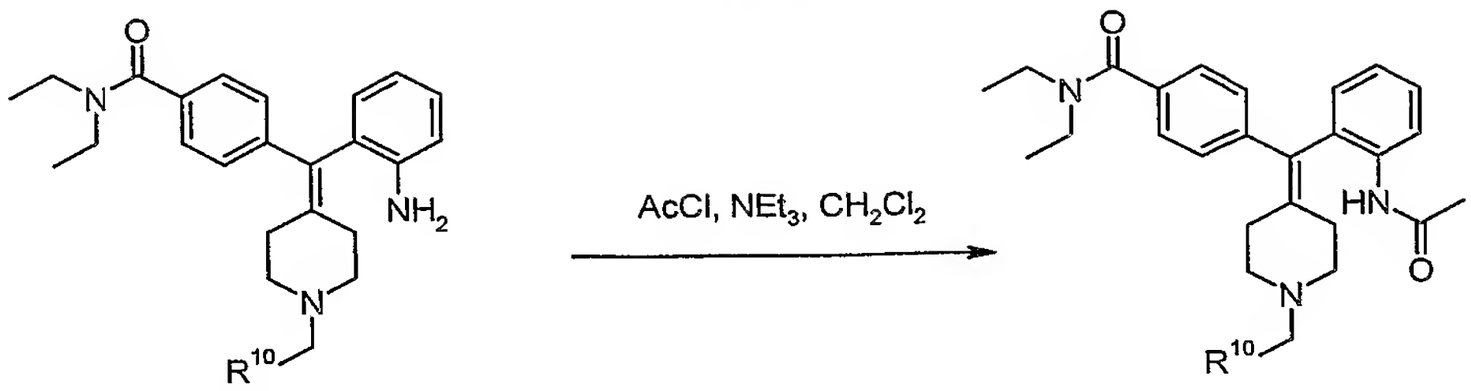
Scheme 15



Intermediate 12 R^{10}=4-pyridyl
Intermediate 13 R^{10}=3-pyridyl

Compound 45 R^{10}=4-pyridyl
Compound 46 R^{10}=3-pyridyl

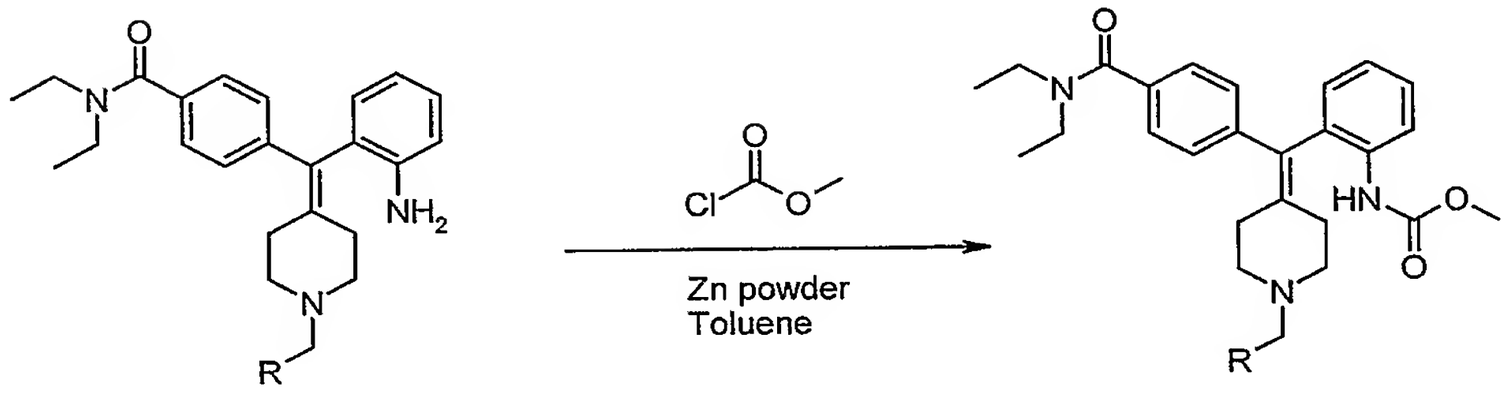
Scheme 16



Compound 41: R^{10}=n-propyl
Compound 44: R^{10}=2-pyridyl

Compound 47: R^{10}=n-propyl
Compound 48: R^{10}=2-pyridyl

Scheme 17

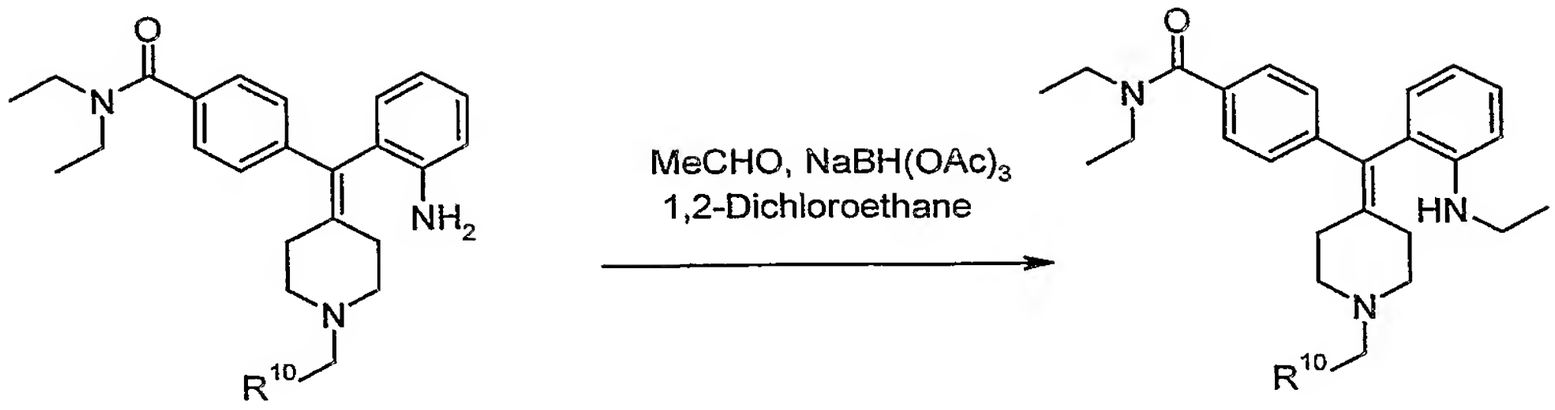


Compound 41 R^{10}=n-propyl
Compound 42 R^{10}=4-pyridyl
Compound 43 R^{10}=3-pyridyl
Compound 44 R^{10}=2-pyridyl

Compound 49 R^{10}=n-propyl
Compound 50 R^{10}=4-pyridyl
Compound 51 R^{10}=3-pyridyl
Compound 52 R^{10}=2-pyridyl

5

Scheme 18



Compound 41 R^{10}=n-propyl
Compound 42 R^{10}=4-pyridyl
Compound 43 R^{10}=3-pyridyl
Compound 44 R^{10}=2-pyridyl

Compound 53 R^{10}=n-propyl
Compound 54 R^{10}=4-pyridyl
Compound 55 R^{10}=3-pyridyl
Compound 56 R^{10}=2-pyridyl

BIOLOGICAL EVALUATION

The compounds of the invention are found to be active towards δ receptors in warm-blooded animal, e.g., human. Particularly the compounds of the invention are found to be effective δ receptor ligands. *In vitro* assays, *infra*, demonstrate these surprising activities, especially with regard to agonists potency and efficacy as demonstrated in the rat brain functional assay and/or the human δ receptor functional assay. This feature may be related to in vivo activity and may not be linearly correlated with binding affinity. In these *in vitro* assays, a compound is tested for their activity toward δ receptors and IC_{50} is obtained to determine the selective activity for a particular compound towards δ receptors. In the current context, IC_{50} generally refers to the concentration of the compound at which 50% displacement of a standard radioactive δ receptor ligand has been observed.

The activities of the compound towards κ and μ receptors are also measured in a similar assay.

In vitro model

Cell culture

Human 293S cells expressing cloned human κ, δ and μ receptors and neomycin resistance are grown in suspension at 37°C and 5% CO_2 in shaker flasks containing calcium-free DMEM10% FBS, 5% BCS, 0.1% Pluronic F-68, and 600 μg/ml geneticin.

Rat brains are weighed and rinsed in ice-cold PBS (containing 2.5mM EDTA, pH 7.4). The brains are homogenized with a polytron for 30 sec (rat) in ice-cold lysis buffer (50mM Tris, pH 7.0, 2.5mM EDTA, with phenylmethylsulfonyl fluoride added just prior use to 0.5MmM from a 0.5M stock in DMSO:ethanol).

Membrane preparation

Cells are pelleted and resuspended in lysis buffer (50 mM Tris, pH 7.0, 2.5 mM EDTA, with PMSF added just prior to use to 0.1 mM from a 0.1 M stock in ethanol), incubated on ice for 15 min, then homogenized with a polytron for 30 sec. The suspension is spun at 1000g (max) for 10 min at 4°C. The supernatant is saved on ice and the pellets resuspended and spun as before. The supernatants from both spins are combined and spun at 46,000 g(max) for 30 min. The pellets are resuspended in cold Tris buffer (50 mM Tris/Cl, pH 7.0) and spun again. The final pellets are resuspended in membrane buffer (50 mM Tris, 0.32 M sucrose, pH 7.0). Aliquots (1 ml) in polypropylene tubes are frozen in dry ice/ethanol and stored at -70°C until use. The protein concentrations are determined by a modified Lowry assay with sodium dodecyl sulfate.

Binding assays

Membranes are thawed at 37°C, cooled on ice, passed 3 times through a 25-gauge needle, and diluted into binding buffer (50 mM Tris, 3 mM $MgCl_2$, 1 mg/ml BSA (Sigma A-7888), pH 7.4, which is stored at 4°C after filtration through a 0.22 m filter, and to which has been freshly added 5 μg/ml aprotinin, 10 μM bestatin, 10 μM

diprotin A, no DTT). Aliquots of 100 µl are added to iced 12x75 mm polypropylene tubes containing 100 µl of the appropriate radioligand and 100 µl of test compound at various concentrations. Total (TB) and nonspecific (NS) binding are determined in the absence and presence of 10 µM naloxone respectively. The tubes are vortexed and incubated at 25°C for 60-75 min, after which time the contents are rapidly vacuum-filtered and washed with about 12 ml/tube iced wash buffer (50 mM Tris, pH 7.0, 3 mM $MgCl_2$) through GF/B filters (Whatman) presoaked for at least 2h in 0.1% polyethyleneimine. The radioactivity (dpm) retained on the filters is measured with a beta counter after soaking the filters for at least 12h in minivials containing 6-7 ml scintillation fluid. If the assay is set up in 96-place deep well plates, the filtration is over 96-place PEI-soaked unifilters, which are washed with 3 x 1 ml wash buffer, and dried in an oven at 55°C for 2h. The filter plates are counted in a TopCount (Packard) after adding 50 µl MS-20 scintillation fluid/well.

Functional Assays

The agonist activity of the compounds is measured by determining the degree to which the compounds receptor complex activates the binding of GTP to G-proteins to which the receptors are coupled. In the GTP binding assay, GTP[γ]^{35}S is combined with test compounds and membranes from HEK-293S cells expressing the cloned human opioid receptors or from homogenised rat and mouse brain. Agonists stimulate GTP[γ]^{35}S binding in these membranes. The EC_{50} and E_{max} values of compounds are determined from dose-response curves. Right shifts of the dose response curve by the delta antagonist naltrindole are performed to verify that agonist activity is mediated through delta receptors. The E_{max} values were determined in relation to the standard δ agonist SNC80, i.e., higher than 100% is a compound that have better efficacy than SNC80.

Procedure for rat brain GTP

Rat brain membranes are thawed at 37°C, passed 3 times through a 25-gauge blunt-end needle and diluted in the GTPγS binding (50 mM Hepes, 20 mM NaOH,

100 mM NaCl, 1 mM EDTA, 5 mM $MgCl_2$, pH 7.4, Add fresh: 1 mM DTT, 0.1% BSA). 120μM GDP final is added membranes dilutions. The EC50 and Emax of compounds are evaluated from 10-point dose-response curves done in 300μl with the appropriate amount of membrane protein (20μg/well) and 100000-130000 dpm of $GTP\gamma^{35}S$ per well (0.11 -0.14nM). The basal and maximal stimulated binding are determined in absence and presence of 3 μM SNC-80

Data analysis

The specific binding (SB) was calculated as TB-NS, and the SB in the presence of various test compounds was expressed as percentage of control SB. Values of IC_{50} and Hill coefficient (n_H) for ligands in displacing specifically bound radioligand were calculated from logit plots or curve fitting programs such as Ligand, GraphPad Prism, SigmaPlot, or ReceptorFit. Values of K_i were calculated from the Cheng-Prussoff equation. Mean ± S.E.M. values of IC_{50}, K_i and n_H were reported for ligands tested in at least three displacement curves.

Based on the above testing protocols, we find that the compounds of the present invention are active toward human δ receptors. Generally, the IC_{50} towards human δ receptor for most compounds of the present invention is in the range of 0.48 nM – 17.9 nM. The EC_{50} and $\%E_{max}$ towards human δ receptor for these compounds are generally in the range of 18.6 nM -1724 nM and 65 – 108, respectively. The IC_{50} towards human κ and μ receptors for the compounds of the invention is generally in the ranges of 1317 nM- 9739 nM and 261 nM – 9774 nM, respectively.

Receptor Saturation Experiments

Radioligand $K\delta$ values are determined by performing the binding assays on cell membranes with the appropriate radioligands at concentrations ranging from 0.2 to 5 times the estimated $K\delta$ (up to 10 times if amounts of radioligand required are feasible). The specific radioligand binding is expressed as pmole/mg membrane

protein. Values of K_δ and B_{max} from individual experiments are obtained from nonlinear fits of specifically bound (B) vs. nM free (F) radioligand from individual according to a one-site model.

Determination Of Mechano-Allodynia Using Von Frey Testing

Testing is performed between 08:00 and 16:00h using the method described by Chaplan et al. (1994). Rats are placed in Plexiglas cages on top of a wire mesh bottom which allows access to the paw, and are left to habituate for 10-15 min. The area tested is the mid-plantar left hind paw, avoiding the less sensitive foot pads. The paw is touched with a series of 8 Von Frey hairs with logarithmically incremental stiffness (0.41, 0.69, 1.20, 2.04, 3.63, 5.50, 8.51, and 15.14 grams; Stoelting, Ill, USA). The von Frey hair is applied from underneath the mesh floor perpendicular to the plantar surface with sufficient force to cause a slight buckling against the paw, and held for approximately 6-8 seconds. A positive response is noted if the paw is sharply withdrawn. Flinching immediately upon removal of the hair is also considered a positive response. Ambulation is considered an ambiguous response, and in such cases the stimulus is repeated.

Testing Protocol

The animals are tested on postoperative day 1 for the FCA-treated group. The 50% withdrawal threshold is determined using the up-down method of Dixon (1980). Testing is started with the 2.04 g hair, in the middle of the series. Stimuli are always presented in a consecutive way, whether ascending or descending. In the absence of a paw withdrawal response to the initially selected hair, a stronger stimulus is presented; in the event of paw withdrawal, the next weaker stimulus is chosen. Optimal threshold calculation by this method requires 6 responses in the immediate vicinity of the 50% threshold, and counting of these 6 responses begins when the first change in response occurs, e.g. the threshold is first crossed. In cases where thresholds fall outside the range of stimuli, values of 15.14 (normal sensitivity) or

0.41 (maximally allodynic) are respectively assigned. The resulting pattern of positive and negative responses is tabulated using the convention, X = no withdrawal; O = withdrawal, and the 50% withdrawal threshold is interpolated using the formula:

$$50\%\ \text{g threshold} = 10^{(Xf + k\delta)} / 10{,}000$$

where Xf = value of the last von Frey hair used (log units); k = tabular value (from Chaplan et al. (1994)) for the pattern of positive / negative responses; and δ = mean difference between stimuli (log units). Here $\delta = 0.224$.

Von Frey thresholds are converted to percent of maximum possible effect (% MPE), according to Chaplan et al. 1994. The following equation is used to compute % MPE:

$$\%\ \text{MPE} = \frac{\text{Drug treated threshold (g) - allodynia threshold (g)}}{\text{Control threshold (g) - allodynia threshold (g)}} \times 100$$

Administration Of Test Substance

Rats are injected (subcutaneously, intraperitoneally, intravenously or orally) with a test substance prior to von Frey testing, the time between administration of test compound and the von Frey test varies depending upon the nature of the test compound.

Writhing Test

Acetic acid will bring abdominal contractions when administered intraperitoneally in mice. These will then extend their body in a typical pattern. When analgesic drugs are administered, this described movement is less frequently observed and the drug selected as a potential good candidate.

A complete and typical Writhing reflex is considered only when the following elements are present: the animal is not in movement; the lower back is slightly depressed; the plantar aspect of *both* paws is observable. In this assay, compounds of the present invention demonstrate significant inhibition of writhing responses after oral dosing of 1-100 μmol/kg.

(i) Solutions preparation

Acetic acid (AcOH): 120 µL of Acetic Acid is added to 19.88 ml of distilled water in order to obtain a final volume of 20 ml with a final concentration of 0.6% AcOH. The solution is then mixed (vortex) and ready for injection.

Compound (drug): Each compound is prepared and dissolved in the most suitable vehicle according to standard procedures.

(ii) Solutions administration

The compound (drug) is administered orally, intraperitoneally (i.p.) , subcutaneously (s.c.) or intravenously (i.v.)) at 10 ml/kg (considering the average mice body weight) 20, 30 or 40 minutes (according to the class of compound and its characteristics) prior to testing. When the compound is delivered centrally: Intraventricularly (i.c.v.) or intrathecally (i.t.) a volume of 5 µL is administered.

The AcOH is administered intraperitoneally (i.p.) in two sites at 10 ml/kg (considering the average mice body weight) immediately prior to testing.

(iii) Testing

The animal (mouse) is observed for a period of 20 minutes and the number of occasions (Writhing reflex) noted and compiled at the end of the experiment. Mice are kept in individual "shoe box" cages with contact bedding. A total of 4 mice are usually observed at the same time: one control and three doses of drug.

For the anxiety and anxiety-like indications, efficacy has been established in the geller-seifter conflict test in the rat.

For the functional gastrointestina disorder indication, efficacy can be established in the assay described by Coutinho SV *et al*, in American Journal of Physiology - Gastrointestinal & Liver Physiology. 282(2):G307-16, 2002 Feb, in the rat.

ADDITIONAL IN VIVO TESTING PROTOCOLS

Subjects and housing

Naïve male Sprague Dawley rats (175-200g) are housed in groups of 5 in a temperature controlled room (22°C, 40-70% humidity, 12-h light/dark). Experiments

are performed during the light phase of the cycle. Animals have food and water ad libitum and are sacrificed immediately after data acquisition.

Sample

Compound (Drug) testing includes groups of rats that do not receive any treatment and others that are treated with E. coli lipopolysaccharide(LPS). For the LPS-treated experiment, four groups are injected with LPS, one of the four groups is then vehicle-treated whilst the other three groups are injected with the drug and its vehicle. A second set of experiments are conducted involving five groups of rats; all of which receive no LPS treatment. The naïve group receives no compound (drug) or vehicle; the other four groups are treated with vehicle with or without drug. These are performed to determine anxiolytic or sedative effects of drugs which can contribute to a reduction in USV.

Administration of LPS

Rats are allowed to habituate in the experimental laboratory for 15-20 min prior to treatment. Inflammation is induced by administration of LPS (endotoxin of gram-negative E. coli bacteria serotype 0111:B4, Sigma). LPS (2.4µg) is injected intracerebro-ventricularly (i.c.v.), in a volume of 10µl, using standard stereotaxic surgical techniques under isoflurane anaesthesia. The skin between the ears is pushed rostrally and a longitudinal incision of about 1cm is made to expose the skull surface. The puncture site is determined by the coordinates: 0.8 mm posterior to the bregma, 1.5 mm lateral (left) to the lambda (sagittal suture), and 5 mm below the surface of the skull (vertical) in the lateral ventricle. LPS is injected via a sterile stainless steel needle (26-G 3/8) of 5 mm long attached to a 100-µl Hamilton syringe by polyethylene tubing (PE20; 10-15 cm). A 4 mm stopper made from a cut needle (20-G) is placed over and secured to the 26-G needle by silicone glue to create the desired 5mm depth.

Following the injection of LPS, the needle remains in place for an additional 10 s to allow diffusion of the compound, then is removed. The incision is closed, and

the rat is returned to its original cage and allowed to rest for a minimum of 3.5h prior to testing.

Experimental setup for air-puff stimulation

The rats remains in the experimental laboratory following LPS injection and compound (drug) administration. At the time of testing all rats are removed and placed outside the laboratory. One rat at a time is brought into the testing laboratory and placed in a clear box (9 × 9 × 18 cm) which is then placed in a sound-attenuating ventilated cubicle measuring 62(w) ×35(d) ×46(h) cm (BRS/LVE, Div. Tech-Serv Inc). The delivery of air-puffs, through an air output nozzlė of 0.32 cm, is controlled by a system (AirStim, San Diego Intruments) capable of delivering puffs of air of fixed duration (0.2 s) and fixed intensity with a frequency of 1 puff per 10s. A maximun of 10 puffs are administered, or until vocalisation starts, which ever comes first. The first air puff marks the start of recording.

Experimental setup for and ultrasound recording

The vocalisations are recorded for 10 minutes using microphones (G.R.A.S. sound and vibrations, Vedbaek, Denmark) placed inside each cubicle and controlled by LMS (LMS CADA-X 3.5B, Data Acquisition Monitor, Troy, Michigan) software. The frequencies between 0 and 32000Hz are recorded, saved and analysed by the same software (LMS CADA-X 3.5B, Time Data Processing Monitor and UPA (User Programming and Analysis)).

Compounds (Drugs)

All compounds (drugs) are pH-adjusted between 6.5 and 7.5 and administered at a volume of 4 ml/kg. Following compound (drug) administration, animals are returned to their original cages until time of testing.

Analysis

The recording is run through a series of statistical and Fourier analyses to filter (between 20-24kHz) and to calculate the parameters of interest. The data are

expressed as the mean ± SEM. Statistical significance is assessed using T-test for comparison between naive and LPS-treated rats, and one way ANOVA followed by Dunnett's multiple comparison test (post-hoc) for drug effectiveness. A difference between groups is considered significant with a minimum p value of ≤0.05. Experiments are repeated a minimum of two times.

EXAMPLES

The invention will further be described in more detail by the following Examples which describe methods whereby compounds of the present invention may be prepared, purified, analyzed and biologically tested, and which are not to be construed as limiting the invention.

INTERMEDIATE 1

A mixture of 4-(bromomethyl)benzoic acid, methyl ester (11.2 g, 49 mmol) and trimethyl phosphite (25 mL) was refluxed under N_2 for 5 hrs. Excess trimethyl phosphite was removed by co-distillation with toluene to give INTERMEDIATE 1 in quantitative yield. ^{1}H NMR ($CDCl_3$) δ 3.20 (d, 2H, J=22 Hz, CH_2), 3.68 (d, 3H 10.8 Hz, OCH_3), 3.78 (d, 3H, 11.2 Hz, OCH_3), 3.91 (s, 3H, OCH_3), 7.38 (m, 2H, Ar-H), 8.00 (d, 2H, J=8 Hz, Ar-H).

INTERMEDIATE 2: 4-(4-Methoxycarbonyl-benzylidene)-piperidine-1-carboxylic acid *tert*-butyl ester

To a solution of INTERMEDIATE 1 in dry THF (200 mL) was added dropwise lithium diisopropylamide (32.7 mL 1.5 M in hexanes, 49 mmol) at -78 °C. The reaction mixture was then allowed to warm to room temperature prior to addition of *N-tert*-butoxycarbonyl-4-piperidone (9.76 g, 49 mmol in 100 mL dry THF). After 12 hrs, the reaction mixture was quenched with water (300 mL) and extracted with

ethyl acetate (3 x 300 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to give a crude product, which was purified by flash chromatography to provide INTERMEDIATE 2 as a white solid (5.64 g, 35%). IR (NaC1) 3424, 2974, 2855, 1718, 1 688, 1606, 1427, 1362, 1276 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 2.31 (t, J=5.5 Hz, 2H), 2.42 (t, J=5.5 Hz, 2H), 3.37 (t, J=5.5 Hz, 2H), 3.48 (t, J=5.5 Hz, 2H), 3.87 (s, 3H, OCH_3), 6.33 (s, 1H, CH), 7.20 (d J=6.7 Hz, 2H, Ar-H), 7.94 (d, J,=6.7 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 28.3, 29.2, 36.19, 51.9, 123.7, 127.8, 128.7, 129.4, 140.5, 142.1, 154.6, 166.8.

INTERMEDIATE 3: 4-Bromo-4-[bromo-(4-methoxycarbonyl-phenyl)-methyl]-piperidine-1-carboxylic acid tert-butyl ester

To a mixture of INTERMEDIATE 2 (5.2 g, 16 mmol) and K_2CO_3 (1.0 g) in dry dichloromethane (200 mL) was added a solution of bromine (2.9 g, 18 mmol) in 30 mL CH_2Cl_2 at 0 °C. after 1.5 hrs at room temperature, the solution after filtration of K_2CO_3 was condensed. The residue was then dissolved in ethyl acetate (200 mL), washed with water (200 mL), 0.5 M HC1 (200 mL) and brine (200 mL), and dried over $MgSO_4$. Removal of solvents provided a crude product, which was recrystallized from methanol to give INTERMEDIATE 3 as a white solid (6.07 g, 78%). IR (NaC1) 3425, 2969, 1725, 1669, 1426, 1365, 1279, 1243 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (s, 9H), 1.75 (m, 1H), 1.90 (m, 1H), 2.1 (m, 2H), 3.08 (br, 2H), 3.90 (s, 3H, OCH_3), 4.08 (br, 3H), 7.57 (d, J=8.4 Hz, 2H, Ar-H) 7.98 (d, J=8.4 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 28.3, 36.6, 38.3, 40.3, 52.1, 63.2, 72.9, 129.0, 130.3, 130.4, 141.9, 154.4, 166.3.

INTERMEDIATE 4: 4-[bromo-(4-carboxy-phenyl)-methylene]-piperidine-1-carboxylic acid tert-butyl ester

A solution of INTERMEDIATE 3 (5.4 g 11 mmol) in methanol (300 mL) and 2.0 M NaOH (100 mL) was heated at 40 °C for 3 hrs. The solid was collected by

filtration, and dried overnight under vacuum. The dry salt was dissolved in 40% acetonitrile/water, and was adjusted to pH 2 using concentrated HCl. INTERMEDIATE 4 (3.8 g, 87%) was isolated as a white powder by filtration. ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H, ^{t}Bu), 2.22 (dd, J=5.5 Hz, 6.1 Hz, 2H), 2.64 (dd, J=5.5 Hz, 6.1 Hz, 2H), 3.34 (dd, J=5.5 Hz, 6.1 Hz, 2H), 3.54 (dd, J=5.5 Hz, 6.1 Hz, 2H), 7.35 (d, J=6.7 Hz, 2H, Ar-H), 8.08 (d, J=6.7 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 28.3, 31.5, 34.2, 44.0, 115.3, 128.7, 129.4, 130.2, 137.7, 145.2, 154.6, 170.3.

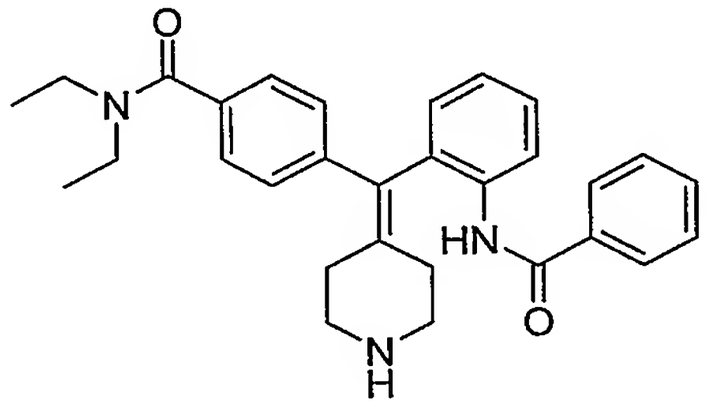
INTERMEDIATE 5: 4-[bromo-(4-diethylcarbamoyl-phenyl)-methylene]-piperidine-1-carboxylic acid tert-butyl ester

To a solution of INTERMEDIATE 4 (1.0 g, 2.5 mmol) in dry dichloromethane (10 mL) at - 20 °C was added isobutylchloroformate (450 mg, 3.3 mmol). After 20 min at -20 °C diethylamine (4 mL) was added and the reaction was allowed to warm to room temperature. After 1.5 hrs the solvents were evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with brine and dried over $MgSO_4$. Removal of solvents provided a crude product, which was purified by flash chromatography to give INTERMEDIATE 5 as white needles (800 mg, 73%). IR (NaCl) 3051, 2975, 1694, 1633, 1416, 1281, 1168, 1115 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.13 (br, 3H, CH_3), 1.22 (br, 3H, CH_3), 1.44 (s, 9H, ^{t}Bu), 2.22 (t, J=5.5 Hz, 2H), 2.62 (t, J=5.5 Hz, 2H), 3.33 (m, 4H), 3.55 (m, 4H), 7.31 (d, J=8.0 Hz, 2H, Ar-H), 7.36 (d, J=8.0 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 12.71, 14.13, 28.3, 31.5, 34.2, 39.1, 43.2, 79.7, 115.9, 126.3, 129.3, 136.8, 137.1, 140.6, 154.6, 170.5.

INTERMEDIATE 6: 4-[(2-aminophenyl)[4-[(diethylamino)carbonyl]phenyl]methylene]- 1-piperidinecarboxylic acid 1,1-dimethylethyl ester

To a mixture of INTERMEDIATE 5 (3.0 g, 6.65 mmol) and 2-aminophenylboronic acid (1.37 g, 9.97 mmol) in toluene (85 mL) and ethanol (17 mL) was added 2.0 M Na_2CO_3 (13 mL). Palladium tetrakistriphenylphosphine (774 mg, 0.1 mmol) was added and the resulting mixture was heated overnight at 90 °C under N_2. The reaction was then concentrated *in vacuo* and the residue was diluted with brine. The aqueous phase was extracted with EtOAc (3x). The combined organic phases was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography, eluting with 7:3 EtOAc:Hexanes, to give INTERMEDIATE 6 as a light brown solid (3.14 g, quantitative yield). ^{1}H NMR (400MHz, $CDCl_3$) δ 1.12 (br s, 3 H), 1.26 (br s, 3 H), 1.46 (s, 9 H), 2.22 (m, 2 H), 2.45 (m, 2 H), 3.28 (br s, 1 H), 3.37 (m, 3 H), 3.54 (m, 4 H), 3.66 (s, 2 H), 6.69 (dd, J=7.91, 0.88 Hz, 1 H), 6.73 (td, J=7.42, 1.17 Hz, 1 H), 6.95 (dd, J=7.71, 1.46 Hz, 1 H), 7.09 (td, J=7.62, 1.56 Hz, 1 H), 7.21 (d, J=8.40 Hz, 2 H), 7.31 (d, J=8.40 Hz, 2 H).

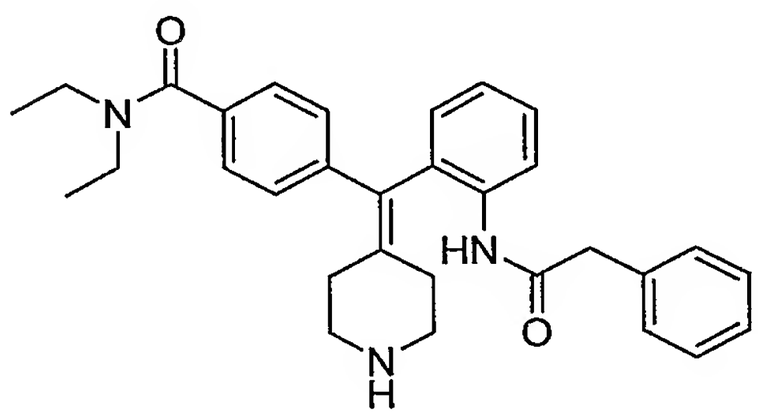
COMPOUND 1: 4-[[2-(benzoylamino)phenyl]-4-piperidinylidenemethyl]-*N*,*N*-diethylbenzamide



To a solution of INTERMEDIATE 6 (400 mg, 0.86 mmol) in CH_2Cl_2 (15 mL) was added triethylamine (0.36 mL, 2.59 mmol) followed by benzoyl chloride (133 mg, 0.95 mmol). The reaction was stirred overnight at room temperature under N_2,

diluted with CH_2Cl_2 and washed with saturated aqueous sodium bicarbonate (1x). The layers were separated and the aqueous layer was extracted with additional CH_2Cl_2 (2x). The combined organic phases was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (15 mL) and trifluoroacetic acid (2.5 mL) was added. The reaction was stirred overnight at room temperature, then concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 10-40% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 1 (275 mg, 46% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 1.06 (t, J=6.64 Hz, 3 H), 1.20 (t, J=6.74 Hz, 3 H), 2.49-2.72 (m, 4 H), 3.10-3.15 (m, 1 H), 3.20-3.31 (m, 4 H), 3.31-3.40 (m, 1 H), 3.43-3.55 (m, 2 H), 7.05 (d, J=8.40 Hz, 2 H), 7.18 (d, J=8.40 Hz, 2 H), 7.27-7.31 (m, 1 H), 7.37-7.43 (m, 3 H), 7.45 (d, J=8.01 Hz, 2 H), 7.55 (tt, J=7.42, 1.37 Hz, 1 H), 7.66 (d, J=7.23 Hz, 2 H). Found: C, 62.61; H, 5.92; N, 6.71. $C_{30}H_{33}N_3O_2$ x 1.2 CF_3CO_2H x 1.0 H_2O has C, 62.52; H, 5.86; N, 6.75 %.

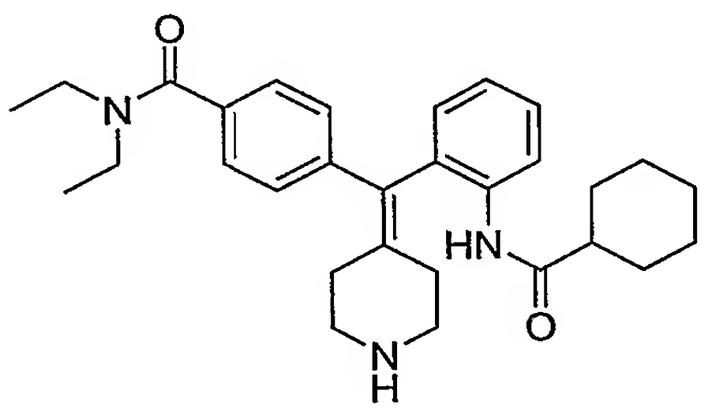
COMPOUND 2: *N*-[2-[[4-[(diethylamino)carbonyl]phenyl]-4-piperidinylidenemethyl]phenyl]benzeneacetamide



Using the same method as for COMPOUND 1 and using INTERMEDIATE 6 (400 mg, 0.86 mmol) and phenylacetyl chloride (133 mg, 0.95 mmol) afforded COMPOUND 2 (381 mg, 62% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400

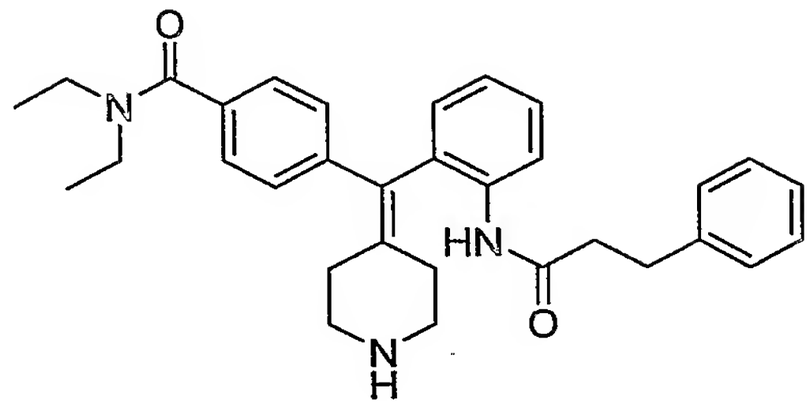
MHz, CD_3OD) δ 1.09 (t, J=6.74 Hz, 3 H), 1.22 (t, J=6.93 Hz, 3 H), 2.34-2.49 (m, 3 H), 2.49-2.59 (m, 1 H), 2.95-3.04 (m, 1 H), 3.09-3.30 (m, 5 H), 3.47-3.58 (overlapping d and m, J=5.66 Hz, 4 H), 6.89 (d, J=8.20 Hz, 2 H), 7.22 (d, J=8.20 Hz, 2 H), 7.26-7.42 (m, 9 H). Found: C, 63.88; H, 6.13; N, 6.66. $C_{30}H_{35}N_3O_2$ x 1.1 CF_3CO_2H x 1.0 H_2O has C, 63.79; H, 6.14; N, 6.72 %.

COMPOUND 3: 4-[[2-[(cyclohexylcarbonyl)amino]phenyl]-4-piperidinylidenemethyl]-*N*,*N*-diethylbenzamide



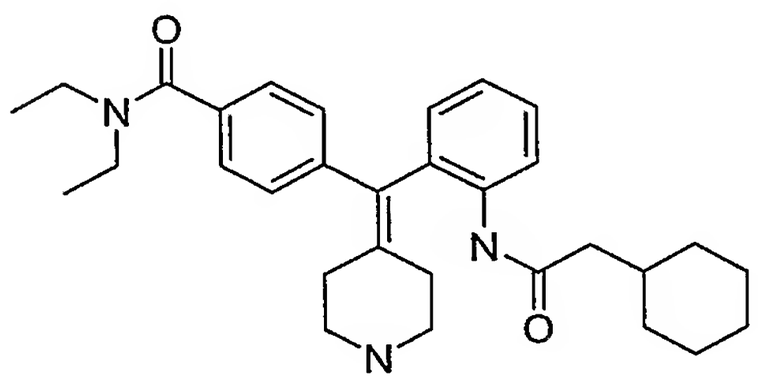
Using the same method as for COMPOUND 1 and using INTERMEDIATE 6 (150 mg, 0.32 mmol) and cyclohexanecarbonyl chloride (52 mg, 0.35 mmol) afforded COMPOUND 3 (159 mg, 83% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 1.04-1.24 (m, 6 H), 1.324-1.39 (m, 4 H), 1.46 (dq, J=12.33, 3.03 Hz, 1 H), 1.58-1.91 (m, 5 H), 2.22 (tt, J=11.28, 3.47 Hz, 1 H), 2.43-2.56 (m, 2 H), 2.61 (dt, J=14.84, 5.86 Hz, 1 H), 2.72 (dt, J=15.04, 6.05 Hz, 1 H), 3.15-3.33 (m, 6 H), 3.47-3.55 (m, J=6.83 Hz, 2 H), 7.19 (d, J=8.40 Hz, 2 H), 7.26-7.34 (m, 6 H). Found: C, 60.51; H, 6.33; N, 6.27. $C_{30}H_{39}N_3O_2$ x 1.6 CF_3CO_2H x 0.2 H_2O has C, 60.45; H, 6.26; N, 6.37 %.

COMPOUND 4: *N*-[2-[[4-[(diethylamino)carbonyl]phenyl]-4-piperidinylidenemethyl]phenyl]benzenepropanamide



Using the same method as for COMPOUND 1 and using INTERMEDIATE 6 (150 mg, 0.32 mmol) and benzenepropanoyl chloride (60 mg, 0.35 mmol) afforded COMPOUND 4 (157 mg, 79% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a beige solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 1.07 (t, J=6.44 Hz, 3 H), 1.21 (t, J=6.64 Hz, 3 H), 2.38-2.59 (m, 5 H), 2.69 (dt, J=15.04, 5.66 Hz, 1 H), 2.79-2.94 (m, 2 H), 3.18-3.31 (m, 6 H), 3.50 (br q, J=6.51 Hz, 2 H), 7.07 (d, J=8.20 Hz, 2 H), 7.15-7.35 (m, 11 H). Found: C, 63.05; H, 5.89; N, 6.50. $C_{32}H_{37}N_3O_2$ x 1.4 CF_3CO_2H x 0.4 H_2O has C, 63.09; H, 5.96; N, 6.34 %.

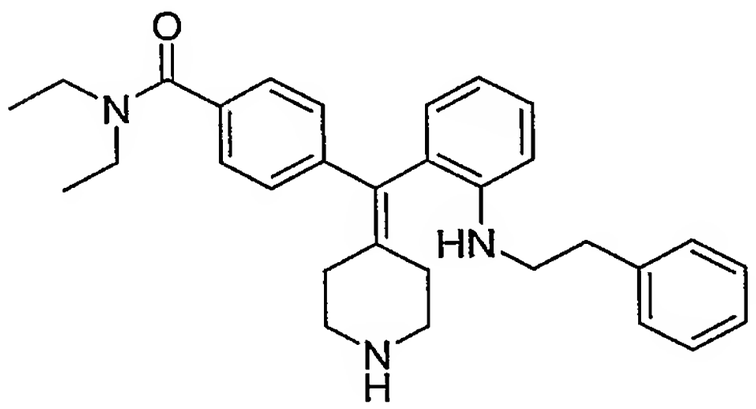
COMPOUND 5: 4-[[2-[(cyclohexylacetyl)amino]phenyl]-4-piperidinylidenemethyl]-*N,N*-diethylbenzamide



To a solution of cyclohexylacetic acid (74 mg, 0.52 mmol) and HATU (172 mg, 0.45 mmol) in DMF (7 mL) was added diisopropylethylamine (0.14 mL, 0.81 mmol), followed by INTERMEDIATE 6 (150 mg, 0.32 mmol). The reaction was stirred overnight at room temperature under N_2, then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with 1N NaOH (1x). The layers were separated and

the aqueous layer was extracted with additional CH_2Cl_2 (2x). The combined organic phases was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography, eluting with 1:1 EtOAc:Hexanes, then redissolved in CH_2Cl_2 (10 mL). Trifluoroacetic acid (1 mL) was added and the reaction was stirred overnight at room temperature. The reaction was concentrated *in vacuo* and the residue was purified by reverse phase HPLC (gradient 10-40% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 5 (130 mg, 67% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 0.90-1.06 (m, 2 H), 1.05-1.33 (m, 9 H), 1.61-1.80 (m, 6 H), 1.97 (dd, J=13.86, 7.23 Hz, 1 H), 2.13 (dd, J=13.86, 6.64 Hz, 1 H), 2.51 (t, J=5.96 Hz, 2 H), 2.61 (ddd, J=14.84, 6.64, 5.27 Hz, 1 H), 2.71 (ddd, J=14.84, 6.83, 5.47 Hz, 1 H), 3.17-3.33 (m, 6 H), 3.51 (q, J=6.64 Hz, 2 H), 7.17 (d, J=8.40 Hz, 2 H), 7.24-7.37 (m, 6 H). Found: C, 61.10; H, 6.47; N, 6.27. $C_{31}H_{41}N_3O_2$ x 1.6 CF_3CO_2H x 0.1 H_2O has C, 61.13; H, 6.42; N, 6.25 %.

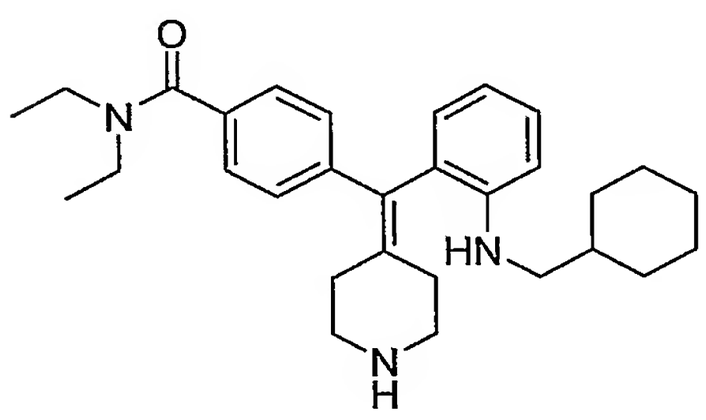
COMPOUND 6: *N,N*-diethyl-4-[[2-[(2-phenylethyl)amino]phenyl]-4-piperidinylidenemethyl]benzamide



To a solution of INTERMEDIATE 6 (300 mg, 0.65 mmol) in 1,2-dichloroethane (20 ml) was added phenylacetaldehyde (156 mg, 1.30 mmol) followed by glacial acetic acid (0.07 mL, 1.30 mmol) and $NaBH(OAc)_3$ (344 mg, 1.63 mmol). The reaction was stirred overnight at room temperature under N_2. Trifluoroacetic acid (2 mL) was added and the reaction was stirred for another 4 hours. The reaction was

diluted with CH_2Cl_2 and washed with saturated aqueous sodium bicarbonate (1x). The layers were separated and the aqueous layer was extracted with additional CH_2Cl_2 (2x). The combined organic phases was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 20-45% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 6 (181 mg, 40% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a beige solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 1.08 (t, J=6.74 Hz, 3 H), 1.21 (t, J=6.83 Hz, 3 H), 2.19-2.36 (m, 2 H), 2.56 (t, J=6.05 Hz, 2 H), 2.84 (t, J=6.64 Hz, 2 H), 2.96-3.05 (m, 1 H), 3.06-3.14 (m, 1 H), 3.13-3.21 (m, 2 H), 3.20-3.30 (m, 2 H), 3.29-3.46 (m, 2 H), 3.46-3.56 (m, 2 H), 6.63 (td, J=7.42, 0.98 Hz, 1 H), 6.73 (d, J=8.20 Hz, 1 H), 6.89 (dd, J=7.42, 1.56 Hz, 1 H), 7.07 (d, J=8.40 Hz, 2 H), 7.10-7.17 (m, 1 H), 7.18-7.27 (m, 5 H), 7.27-7.33 (m, 2 H). Found: C, 65.55; H, 6.48; N, 6.69. $C_{31}H_{37}N_3O$ x 1.2 CF_3CO_2H x 0.4 H_2O has C, 65.58; H, 6.43; N, 6.87 %.

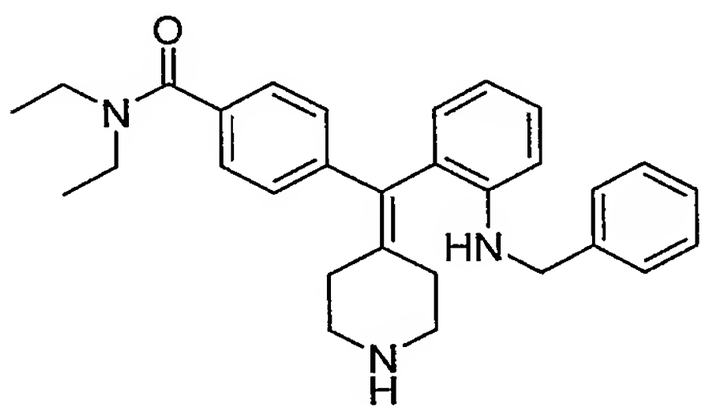
COMPOUND 7: 4-[[2-[(cyclohexylmethyl)amino]phenyl]-4-piperidinylidenemethyl]-*N*,*N*-diethylbenzamide



To a solution of INTERMEDIATE 6 (300 mg, 0.65 mmol) in 1,2-dichloroethane (20 ml) was added cyclohexanecarboxaldehyde (146 mg, 1.30 mmol) followed by glacial acetic acid (0.07 mL, 1.30 mmol) and $NaBH(OAc)_3$ (344 mg, 1.63 mmol). The reaction was stirred overnight at room temperature under N_2. Trifluoroacetic acid (2 mL) was added and the reaction was stirred for another 4 hours. The reaction was diluted with CH_2Cl_2 and washed with saturated aqueous

sodium bicarbonate (1x). The layers were separated and the aqueous layer was extracted with additional CH_2Cl_2 (2x). The combined organic phases was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 20-50% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 7 (190 mg, 43% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 0.78-0.90 (m, 2 H), 1.05-1.25 (m, 10 H), 1.41-1.52 (m, 1 H), 1.52-1.72 (m, 5 H), 2.36-2.50 (m, 2 H), 2.64-2.77 (m, 2 H), 2.88 (d, J=6.64 Hz, 2 H), 3.12-3.38 (m, 5 H), 3.46-3.55 (m, 2 H), 6.59-6.66 (m, 2 H), 6.96 (dd, J=7.42, 1.37 Hz, 1 H), 7.12 (ddd, J=8.70, 7.42, 1.56 Hz, 1 H), 7.31 (s, 4 H). Found: C, 63.61; H, 6.86; N, 6.92. $C_{30}H_{41}N_3O$ x 1.4 CF_3CO_2H has C, 63.61; H, 6.90; N, 6.78 %.

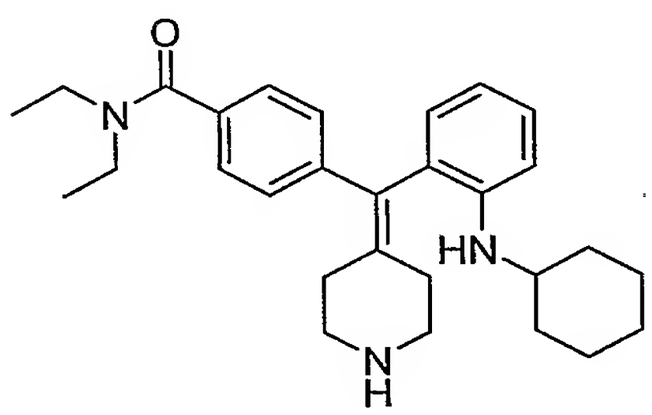
COMPOUND 8: *N,N*-diethyl-4-[[2-[(phenylmethyl)amino]phenyl]-4-piperidinylidenemethyl]-benzamide



To a solution of INTERMEDIATE 6 (309 mg, 0.67 mmol) in 1,2-dichloroethane (20 ml) was added benzaldehyde (140 µL, 1.38 mmol) followed by glacial acetic acid (38 µL, 0.66 mmol) and $NaBH(OAc)_3$ (283 mg, 1.34 mmol). The reaction was stirred overnight at room temperature under N_2. Trifluoroacetic acid (2 mL) was added and the reaction was stirred for another 4 hours. The reaction was diluted with CH_2Cl_2 and washed with saturated aqueous sodium bicarbonate (1x). The layers were separated and the aqueous layer was extracted with additional CH_2Cl_2 (2x). The combined organic phases was dried over Na_2SO_4, filtered and concentrated

in vacuo. The residue was purified by reverse phase HPLC (gradient 20-50% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 8 (203 mg, 45% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 1.11 (br t, J = 7.62 Hz, 3H), 1.24 (br t, J = 7.62 Hz, 3H), 2.46-2.52 (m, 2H), 2.64-2.79 (m, 2H), 3.17-3.37 (m, 6H), 3.49-3.58 (m, 2H), 4.34 (s, 2H), 6.54-6.57 (m, 1H), 6.61-6.66 (m, 1H), 6.96 (dd, J = 7.62, 1.56 Hz, 1H), 7.01-7.08 (m, 1H), 7.11-7.27 (m, 5H), 7.32-7.37 (m, 4H). Found: C, 62.71; H, 5.89; N, 6.74. $C_{30}H_{35}N_3O$ x 1.5 CF_3CO_2H x 0.4 H_2O has C, 62.73; H, 5.95; N, 6.65%

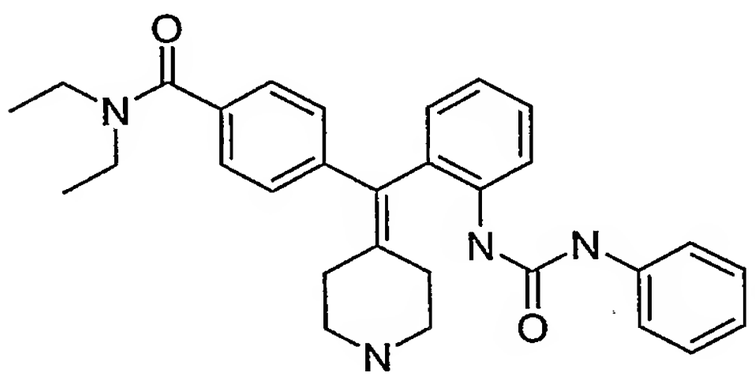
COMPOUND 9: 4-[[2-(cyclohexylamino)phenyl]-4-piperidinylidenemethyl]-*N,N*-diethylbenzamide



To a suspension of INTERMEDIATE 6 (200 mg, 0.43 mmol) and cyclohexanone (47 mg, 0.47 mmol) in MeOH (6 mL) was added decaborane (16 mg, 0.3 mmol). The reaction was stirred overnight at room temperature under N_2, then concentrated *in vacuo*. The residue was filtered through a short plug of silica gel eluting with 1:1 EtOAc:Hexanes and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and trifluoroacetic acid (1.5 mL) was added. The reaction was stirred overnight at room temperature, then concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 10-40% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 9 (207 mg, 71% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a colorless

solid. Purity (HPLC): > 99%; ^{1}H NMR (400 MHz, CD_3OD) δ 0.69-0.82 (m, 1 H), 1.05-1.38 (m, 11 H), 1.47-1.61 (m, 2 H), 1.69 (d, J=12.89 Hz, 2 H), 1.93 (d, J=11.72 Hz, 1 H), 2.37-2.51 (m, 2 H), 2.66-2.81 (m, 2 H), 3.08-3.17 (m, 1 H), 3.17-3.38 (m, 5 H), 3.51 (br q, J=6.45 Hz, 2 H), 6.73-6.79 (m, 2 H), 7.06 (dd, J=7.62, 1.56 Hz, 1 H), 7.18 (ddd, J=8.25, 7.37, 1.56 Hz, 1 H), 7.28-7.36 (m, 4 H). Found: C, 58.94; H, 6.47; N, 6.31. $C_{29}H_{39}N_3O$ x 1.8 CF_3CO_2H x 0.7 H_2O has C, 59.01; H, 6.41; N, 6.33 %.

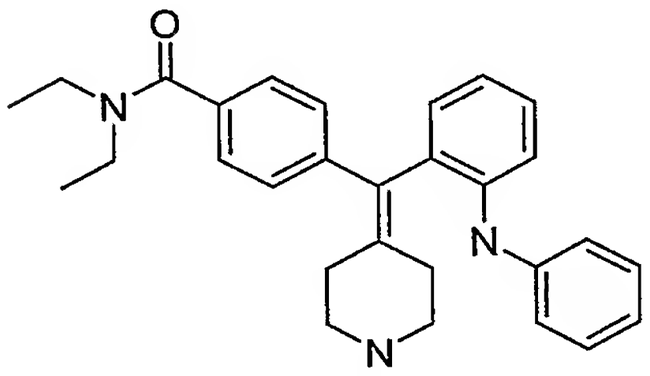
COMPOUND 10: *N,N*-diethyl-4-[[2-[[(phenylamino)carbonyl]amino]phenyl]-4-piperidinylidenemethyl]benzamide



A solution of INTERMEDIATE 6 (200 mg, 0.43 mmol) and phenyl isocyanate (56 mg, 0.47 mmol) in 1,2-dichloroethane (10 ml) was stirred overnight at 70 °C under N_2. The reaction was then diluted with CH_2Cl_2 and washed with saturated aqueous sodium bicarbonate (1x). The layers were separated and the aqueous layer was extracted with additional CH_2Cl_2 (2x). The combined organic phases was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and trifluoroacetic acid (1.5 mL) was added. The reaction was stirred for 6 hours at room temperature, then concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 10-40% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 10 (235 mg, 92% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^{1}H NMR (400 MHz, CD_3OD) δ 0.97 (t, J=6.74 Hz, 3 H), 1.17 (t, J=7.03 Hz, 3 H), 2.48 (t, J=6.05 Hz, 2 H), 2.68 (q, J=5.60 Hz, 2 H), 3.04-

3.15 (m, 2 H), 3.15-3.27 (m, 4 H), 3.39-3.53 (m, 2 H), 6.98 (tt, J=7.22, 1.17 Hz, 1 H), 7.16 (td, J=7.42, 1.37 Hz, 1 H), 7.20-7.28 (m, 6 H), 7.28-7.30 (m, 1 H), 7.30 (dd, J=1.76, 0.98 Hz, 1 H), 7.33-7.34 (m, 1 H), 7.34-7.37 (m, 1 H), 7.60 (dd, J=8.10, 0.88 Hz, 1 H). Found: C, 57.39; H, 5.32; N, 7.87. $C_{30}H_{34}N_4O_2$ x 1.9 CF_3CO_2H x 0.5 H_2O has C, 57.32; H, 5.25; N, 7.91 %.

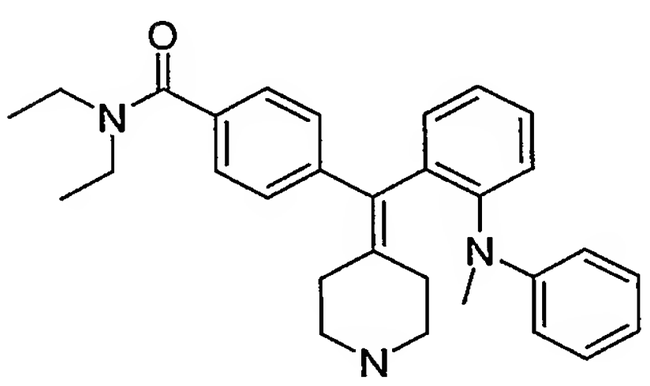
COMPOUND 11: *N,N*-diethyl-4-[[2-(phenylamino)phenyl]-4-piperidinylidenemethyl]benzamide



A mixture of INTERMEDIATE 6 (300 mg, 0.65 mmol), bromobenzene (133 mg, 0.85 mmol), $Pd_2(dba)_3$ (24 mg, 0.026 mmol), NaO^tBu (87 mg, 0.91 mmol), (±)-BINAP (32 mg, 0.052 mmol) in toluene (3.7 mL) was contained in a microwave process vial. The vial was flushed with N_2, capped and heated to 110 °C for 5 min using microwave irradiation. The resulting mixture was cooled, concentrated *in vacuo*, then purified by silica gel column chromatography, eluting with 2:3 EtOAc:Hexanes. The product was dissolved in CH_2Cl_2 (20 mL) and trifluoroacetic acid (2 mL) was added. The reaction was stirred overnight at room temperature then concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 15-40% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 11 (193 mg, 44% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 1.01 (t, J=6.83 Hz, 3 H), 1.19 (t, J=7.03 Hz, 3 H), 2.48-2.58 (m, 2 H), 2.58-2.76 (m, 2 H), 3.03 (q, J=6.83 Hz, 2 H), 3.11-3.26 (m, 4 H), 3.46 (q, J=7.03 Hz, 2 H), 6.71-6.79

(m, 3 H), 6.98 (ddd, J=7.62, 6.25, 2.34 Hz, 1 H), 7.05-7.11 (m, 2 H), 7.16-7.24 (m, 7 H). Found: C, 65.08; H, 6.11; N, 7.20. $C_{29}H_{33}N_3O$ x 1.1 CF_3CO_2H x 0.6 H_2O has C, 65.08; H, 6.18; N, 7.30 %.

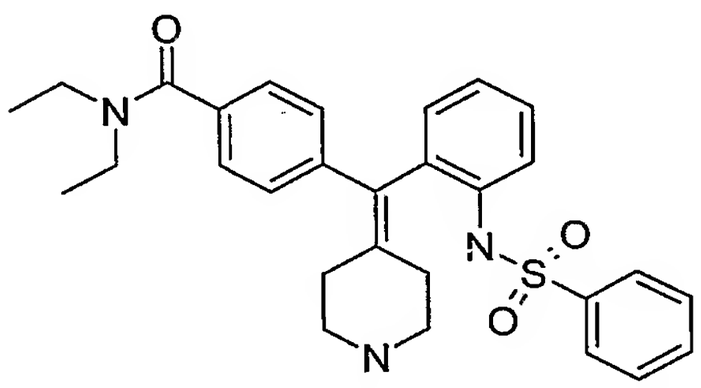
COMPOUND 12: *N,N*-diethyl-4-[[2-(methylphenylamino)phenyl]-4-piperidinylidenemethyl]benzamide



A mixture of INTERMEDIATE 6 (225 mg, 0.49 mmol), bromobenzene (99 mg, 0.63 mmol), $Pd_2(dba)_3$ (18 mg, 0.019 mmol), NaO^tBu (65 mg, 0.68 mmol), (±)-BINAP (24 mg, 0.039 mmol) in toluene (2.8 mL) was contained in a microwave process vial. The vial was flushed with N_2, capped and heated to 110 °C for 5 min using microwave irradiation. The resulting mixture was cooled, concentrated *in vacuo*, then purified by silica gel column chromatography, eluting with 2:3 EtOAc:Hexanes. The product (260 mg, 0.48 mmol) was dissolved in DMF (11 mL) and sodium hydride (46 mg, 1.16 mmol) was added. The reaction was stirred for 1 hour at room temperature. Methyl iodide (171 mg, 1.21 mmol) was then added and the reaction was stirred overnight at room temperature. After 18 hours, the reaction was quenched with saturated ammonium chloride and extracted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with additional CH_2Cl_2 (2x). The combined organic phases was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and trifluoroacetic acid was added (1.5 mL). The reaction was stirred overnight at room temperature then concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 20-

50% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 12 (126 mg, 34% yield over two steps) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a pale yellow solid. Purity (HPLC): 91% (215 nm), 93% (254 nm), 86% (280 nm); ^1H NMR (400 MHz, CD_3OD) δ 1.04 (br s, 3 H), 1.19 (br s, 3 H), 2.38-2.57 (m, 3 H), 2.57-2.72 (m, 4 H), 2.93-3.18 (m, 5 H), 3.20-3.33 (m, 1 H), 3.48 (br s, 2 H), 6.27 (d, J=8.20 Hz, 2 H), 6.60 (t, J=7.32 Hz, 1 H), 6.92 (d, J=8.01 Hz, 2 H), 7.01 (t, J=7.81 Hz, 2 H), 7.13 (d, J=7.62 Hz, 1 H), 7.16-7.23 (m, 2 H), 7.34 (t, J=7.03 Hz, 1 H), 7.43 (dd, J=14.65, 7.42 Hz, 2 H).

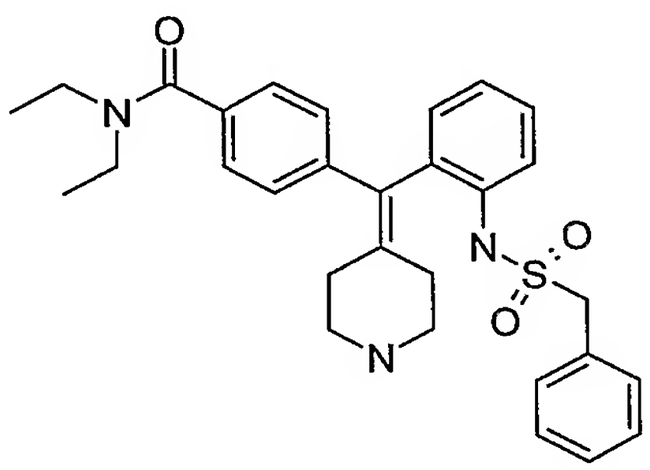
COMPOUND 13: *N,N*-diethyl-4-[[2-[(phenylsulfonyl)amino]phenyl]-4-piperidinylidenemethyl]benzamide



To a solution of INTERMEDIATE 6 (300 mg, 0.65 mmol) in pyridine (10 ml) was added benzenesulfonyl chloride (230 mg, 1.30 mmol). The reaction was stirred overnight at room temperature under N_2, then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with saturated aqueous sodium bicarbonate (1x). The layers were separated and the aqueous layer was extracted with additional CH_2Cl_2 (2x). The combined organic phases was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (15 mL) and trifluoroacetic acid (2.0 mL) was added. The reaction was stirred overnight at room temperature, then concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 10-40% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 13 (298 mg, 63% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O

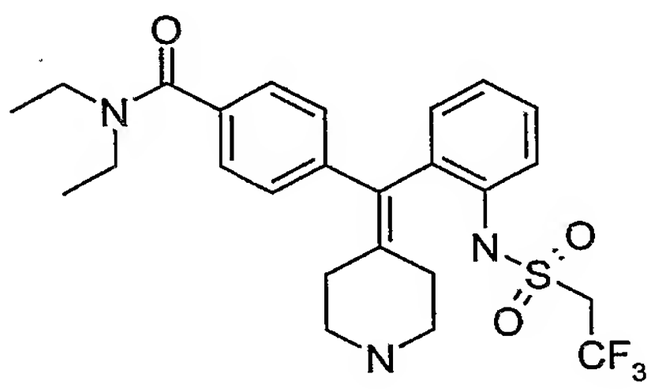
to produce a yellow solid. Purity (HPLC): > 99%; ^{1}H NMR (400 MHz, CD_3OD) δ 1.11 (t, J=6.64 Hz, 3 H), 1.22 (t, J=7.03 Hz, 3 H), 2.43-2.52 (m, 1 H), 2.52-2.61 (m, 2 H), 2.72-2.83 (m, 1 H), 3.22-3.36 (m, 5 H), 3.38-3.48 (m, 1 H), 3.47-3.60 (m, 2 H), 6.64 (dd, J=8.01, 0.78 Hz, 1 H), 7.11 (ddd, J=8.01, 7.03, 1.95 Hz, 1 H), 7.1-7.34 (m, 6 H), 7.48-7.53 (m, 2 H), 7.60 (tt, J=7.42, 1.37 Hz, 1 H), 7.64-7.69 (m, 2 H). Found: C, 58.37; H, 5.58; N, 6.46. $C_{29}H_{33}N_3O_3S$ x 1.1 CF_3CO_2H x 0.7 H_2O has C, 58.40; H, 5.58; N, 6.55 %.

COMPOUND 14: *N,N*-diethyl-4-[[2-[[(phenylmethyl)sulfonyl]amino]phenyl]-4-piperidinylidenemethyl]benzamide



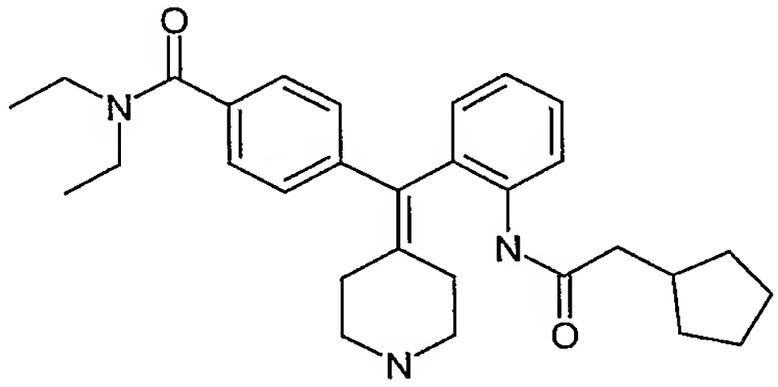
Using the same method as for COMPOUND 13 and using INTERMEDIATE 6 (250 mg, 0.54 mmol) and benzylsulfonyl chloride (206 mg, 1.08 mmol) afforded COMPOUND 14 (253 mg, 63% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a beige solid. Purity (HPLC): > 99%; ^{1}H NMR (400 MHz, CD_3OD) δ 1.02 (t, J=6.83 Hz, 3 H), 1.20 (t, J=6.64 Hz, 3 H), 2.36-2.52 (m, 2 H), 2.52-2.62 (m, 1 H), 2.74 (dt, J=15.38, 5.40 Hz, 1 H), 3.13-3.27 (m, 5 H), 3.30-3.39 (m, 1 H), 3.42-3.55 (m, 2 H), 4.13 (d, J=13.86 Hz, 1 H), 4.25 (d, J=13.67 Hz, 1 H), 7.17 (dt, J=7.22, 1.17 Hz, 1 H), 7.22-7.36 (m, 12 H). Found: C, 58.87; H, 5.76; N, 6.31. $C_{30}H_{35}N_3O_3S$ x 1.1 CF_3CO_2H x 0.8 H_2O has C, 58.82; H, 5.78; N, 6.39 %.

COMPOUND 15: *N,N*-Diethyl-4-[4-piperidinylidene[2-[[(2,2,2-trifluoroethyl)sulfonyl]amino]phenyl]methyl]benzamide



Using the same method as for COMPOUND 13 and using INTERMEDIATE 6 (203 mg, 0.44 mmol) and 2,2,2-trifluoroethanesulfonyl chloride (0.097 mL, 0.88 mmol) afforded COMPOUND 15 (244 mg, 89% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a slightly yellow solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 1.11 (br t, J=6.6 Hz, 3 H), 1.23 (br t, J=7.0 Hz, 3 H), 2.42-2.59 (m, 3 H), 2.73-2.82 (m, 1 H), 3.19-3.40 (m, 6 H), 3.53 (q, J=6.8 Hz, 2 H), 3.95-4.15 (m, 2 H), 7.26-7.44 (m, 8 H).

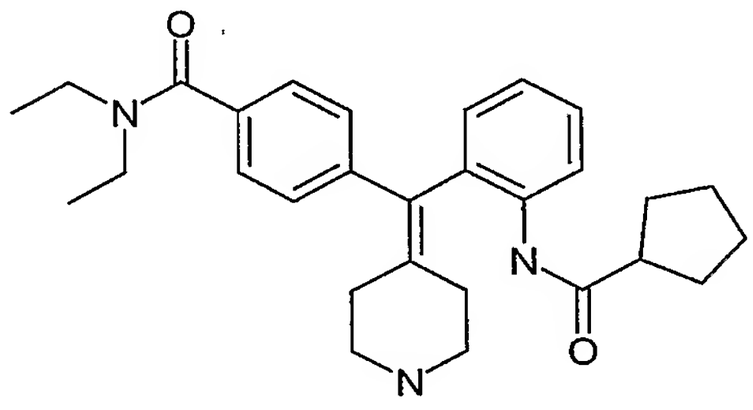
COMPOUND 16: 4-[{2-[(cyclopentylacetyl)amino]phenyl}(piperidin-4-ylidene)methyl]-*N,N*-diethylbenzamide



Using the same method as for COMPOUND 1 and using INTERMEDIATE 6 (175 mg, 0.377 mmol) and cyclopentylacetyl chloride (61 mg, 0.415 mmol) afforded COMPOUND 16 (180 mg, 81%) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400

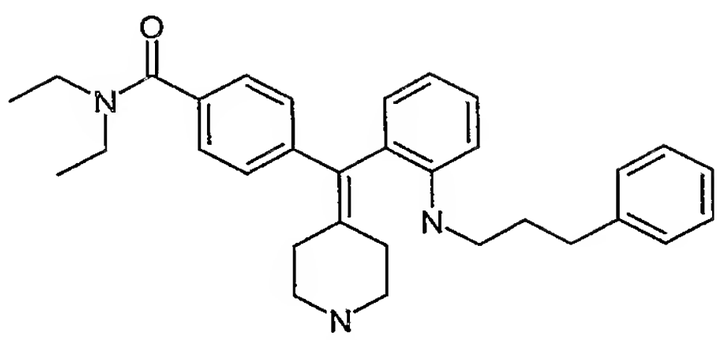
MHz, CD_3OD) δ 1.06-1.26 (m, 8 H), 1.49-1.70 (m, 4 H), 1.72-1.87 (m, 2 H), 2.08-2.31 (m, 3 H), 2.52 (t, J=5.96 Hz, 2 H), 2.56-2.66 (m, 1 H), 2.67-2.78 (m, 1 H), 3.16-3.34 (m, 6 H), 3.46-3.56 (br q, J=6.83 Hz, 2 H), 7.17 (d, J=8.40 Hz, 2 H), 7.26-7.37 (m, 6 H). Found: C, 63.19; H, 6.90; N, 6.59. $C_{30}H_{39}N_3O_2$ x 1.1 CF_3CO_2H x 0.7 H_2O has C, 63.23; H, 6.84; N, 6.87 %.

COMPOUND 17: 4-[{2-[(cyclopentylcarbonyl)amino]phenyl}(piperidin-4-ylidene)methyl]-*N*,*N*-diethylbenzamide



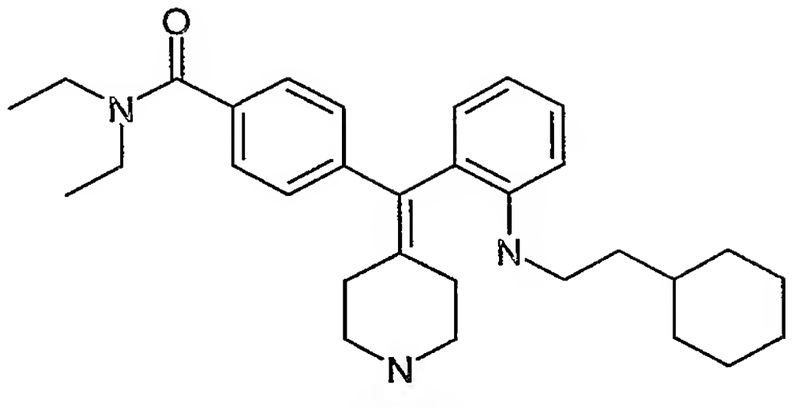
Using the same method as for COMPOUND 1 and using INTERMEDIATE 6 (145 mg, 0.313 mmol) and cyclopentanecarbonyl chloride (46 mg, 0.344 mmol) afforded COMPOUND 17 (141 mg, 79%) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 1.10 (br t, J=6.35 Hz, 3 H), 1.21 (br t, J=6.35 Hz, 3 H), 1.44-1.86 (m, 7 H), 1.87-1.99 (m, 1 H), 2.47-2.54 (m, 2 H), 2.55-2.79 (m, 3 H), 3.16-3.34 (m, 6 H), 3.51 (br q, J=7.16 Hz, 2 H), 7.18 (d, J=8.40 Hz, 2 H), 7.27-7.35 (m, 6 H). Found: C, 60.05; H, 6.05; N, 6.71. $C_{29}H_{37}N_3O_2$ x 1.6 CF_3CO_2H x 0.1 H_2O has C, 60.07; H, 6.07; N, 6.53 %.

COMPOUND 18: *N*,*N*-diethyl-4-[{2-[(3-phenylpropyl)amino]phenyl}(piperidin-4-ylidene)methyl]benzamide



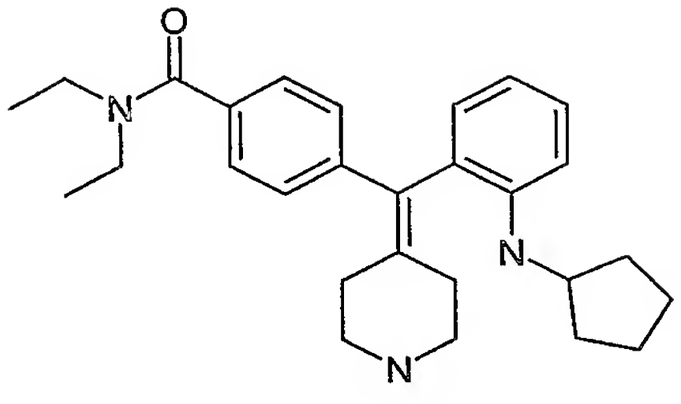
To a solution of INTERMEDIATE 6 (200 mg, 0.43 mmol) in 1,2-dichloroethane (13 ml) was added 3-phenylpropionaldehyde (93 mg, 0.69 mmol) followed by glacial acetic acid (39 μL, 0.69 mmol) and $NaBH(OAc)_3$ (183 mg, 0.86 mmol). The reaction was stirred overnight at room temperature under N_2. Trifluoroacetic acid (1.5mL) was added and the reaction was overnight at room temperature. The reaction was diluted with CH_2Cl_2 and washed with saturated aqueous sodium bicarbonate (1x). The layers were separated and the aqueous layer was extracted with additional CH_2Cl_2 (2x). The combined organic phases was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 20-50% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 18 (112 mg, 37% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 0.99 (br t, J=6.69 Hz, 3 H), 1.18 (br t, J=6.64 Hz, 3 H), 1.71-1.81 (m, 2 H), 2.37-2.56 (m, 4 H), 2.64-2.79 (m, 2 H), 3.00-3.27 (m, 7 H), 3.30-3.37 (m, 1 H), 3.48 (br q, J=6.58 Hz, 2 H), 6.60 (d, J=7.71 Hz, 1 H), 6.66 (dt, J=7.42, 0.98 Hz, 1 H), 6.98 (dd, J=7.47, 1.61 Hz, 1 H), 7.04-7.08 (m, 2 H), 7.10-7.15 (m, 2 H), 7.18-7.24 (m, 2 H), 7.29-7.35 (m, 4 H). Found: C, 62.11; H, 5.88; N, 5.69. $C_{32}H_{39}N_3O$ x 1.8 CF_3CO_2H x 0.1 H_2O has C, 62.08; H, 6.00; N, 6.10 %.

COMPOUND 19: 4-[{2-[(2-cyclohexylethyl)amino]phenyl}(piperidin-4-ylidene)methyl]-*N*,*N*-diethylbenzamide



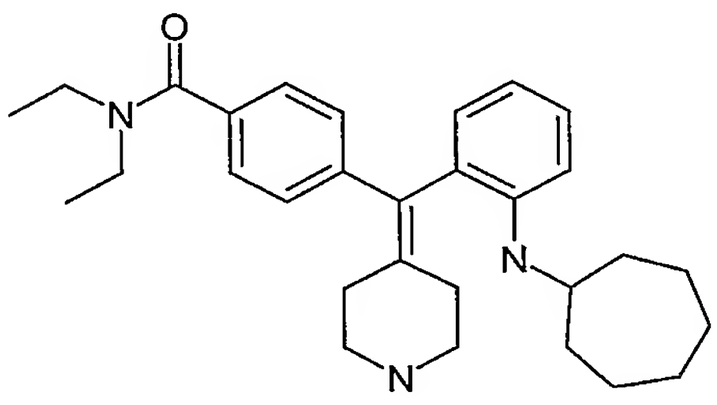
To a solution of INTERMEDIATE 6 (175 mg, 0.377 mmol) in 1,2-dichloroethane (12 ml) was added cyclohexylacetaldehyde (57 mg, 0.453 mmol) followed by glacial acetic acid (26 μL, 0.453 mmol) and $NaBH(OAc)_3$ (160 mg, 0.755 mmol). The reaction was stirred overnight at room temperature under N_2. Trifluoroacetic acid (1.5mL) was added and the reaction was overnight at room temperature. The reaction was diluted with CH_2Cl_2 and washed with saturated aqueous sodium bicarbonate (1x). The layers were separated and the aqueous layer was extracted with additional CH_2Cl_2 (2x). The combined organic phases was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 20-50% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 19 (89 mg, 34% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 0.85-0.98 (m, 2 H), 1.10 (br t, J=6.25 Hz, 3 H), 1.04-1.32 (m, 4 H), 1.21 (br t, J=7.08 Hz, 3 H), 1.32-1.44 (m, 2 H), 1.59-1.75 (m, 5 H), 2.35-2.48 (m, 2 H), 2.63-2.76 (m, 2 H), 3.01-3.36 (m, 8 H), 3.48-3.56 (m, 2 H), 6.62-6.68 (m, 2 H), 6.94 (dd, J=7.37, 1.32 Hz, 1 H), 7.14 (ddd, J=8.30, 7.42, 1.66 Hz, 1 H), 7.29-7.35 (m, 4 H). Found: C, 64.57; H, 7.10; N, 6.95. $C_{31}H_{43}N_3O$ x 1.3 CF_3CO_2H x 0.2 H_2O has C, 64.52; H, 7.20; N, 6.72 %.

COMPOUND 20: 4-[[2-(cyclopentylamino)phenyl](piperidin-4-ylidene)methyl]-*N,N*-diethylbenzamide



Using the same method as for COMPOUND 9 and using INTERMEDIATE 6 (200 mg, 0.43 mmol) and cyclopentanone (40 mg, 0.47 mmol) afforded COMPOUND 20 (210 mg, 74%) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 1.05-1.26 (m, 1 H), 1.09 (br t, J=6.06 Hz, 3 H), 1.21 (t, J=6.64 Hz, 3 H), 1.30-1.67 (m, 5 H), 1.71-1.81 (m, 1 H), 1.90-2.02 (m, 1 H), 2.36-2.52 (m, 2 H), 2.65-2.79 (m, 2 H), 3.14-3.36 (m, 6 H), 3.47-3.55 (m, 2 H), 3.66-3.74 (m, 1 H), 6.69-6.76 (m, 2 H), 7.02 (dd, J=7.32, 1.27 Hz, 1 H), 7.16 (ddd, J=8.45, 7.18, 1.76 Hz, 1 H), 7.27-7.35 (m, 4 H). Found: C, 56.62; H, 5.62; N, 6.30. $C_{28}H_{37}N_3O$ x 2.2 CF_3CO_2H x 0.2 H_2O has C, 56.72; H, 5.82; N, 6.12 %.

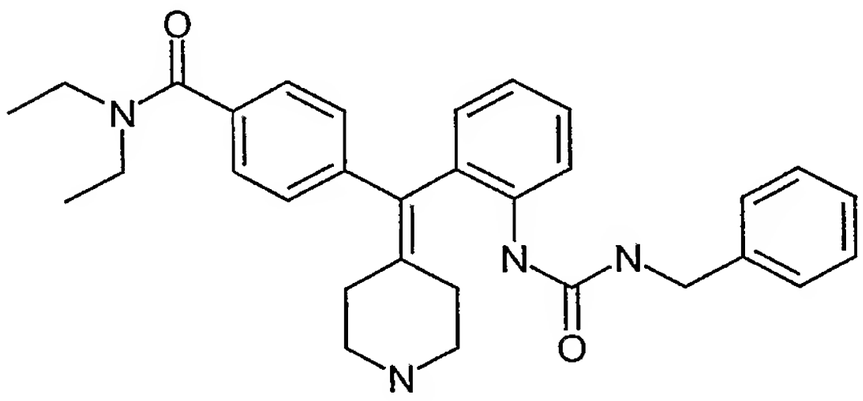
COMPOUND 21: 4-[[2-(cycloheptylamino)phenyl](piperidin-4-ylidene)methyl]-*N,N*-diethylbenzamide



Using the same method as for COMPOUND 9 and using INTERMEDIATE 6 (200 mg, 0.43 mmol) and cycloheptanone (53 mg, 0.47 mmol) afforded COMPOUND 21 (241 mg, 81%) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400

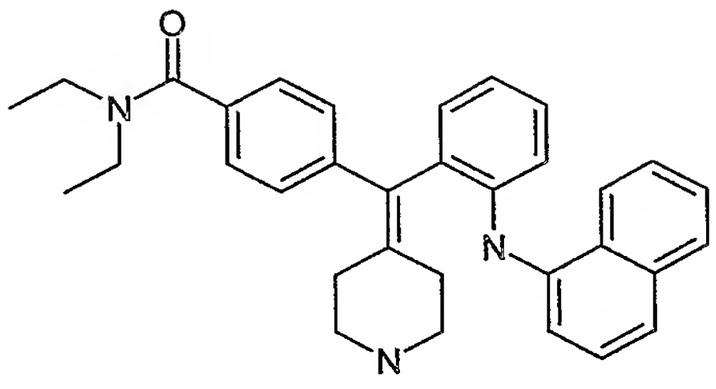
MHz, CD_3OD) δ 1.05-1.25 (m, 4 H), 1.21 (t, J=7.03 Hz, 3 H), 1.25-1.70 (m, 11 H), 1.8-1.98 (m, 1 H), 2.36-2.49 (m, 2 H), 2.67-2.80 (m, 2 H), 3.13-3.38 (m, 6 H), 3.51 (q, J=6.70 Hz, 2 H), 6.71 (d, J=8.01 Hz, 1 H), 6.77 (dt, J=7.42, 1.17 Hz, 1 H), 7.06 (dd, J=7.62, 1.37 Hz, 1 H), 7.19 (dq, J=7.42, 1.56 Hz, 1 H), 7.27-7.35 (m, 4 H). Found: C, 57.47; H, 5.91; N, 5.76. $C_{30}H_{41}N_3O$ x 2.3 CF_3CO_2H x 0.1 H_2O has C, 57.42; H, 6.06; N, 5.81 %.

COMPOUND 22: 4-[(2-{[(benzylamino)carbonyl]amino}phenyl)(piperidin-4-ylidene)methyl]-*N*,*N*-diethylbenzamide



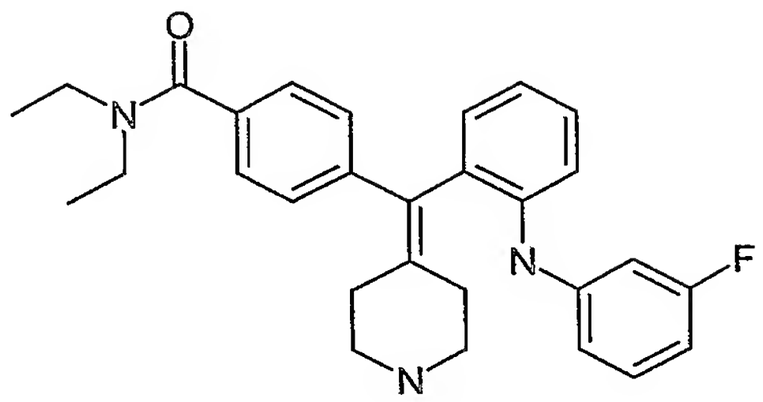
Using the same method as for COMPOUND 10 and using INTERMEDIATE 6 (200 mg, 0.43 mmol) and benzyl isocyanate (63 mg, 0.47 mmol) afforded COMPOUND 22 (193 mg, 74%) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a beige solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 1.08 (t, J=6.64 Hz, 3 H), 1.23 (t, J=6.64 Hz, 3 H), 2.44 (t, J=6.05 Hz, 2 H), 2.55-2.68 (m, 2 H), 3.12-3.27 (m, 6 H), 3.51 (br q, J=6.44 Hz, 2 H), 4.23-4.36 (m, 2 H), 7.13 (dt, J=7.42, 1.37 Hz, 1 H), 7.17-7.21 (m, 3 H), 7.22-7.36 (m, 8 H), 7.56 (dd, J=8.20, 0.78 Hz, 1 H). Found: C, 62.35; H, 5.96; N, 8.73. $C_{31}H_{36}N_4O_2$ x 1.2 CF_3CO_2H x 0.5 H_2O has C, 62.44; H, 5.99; N, 8.72 %.

COMPOUND 23: *N*,*N*-diethyl-4-[[2-(1-naphthylamino)phenyl](piperidin-4-ylidene)methyl]benzamide



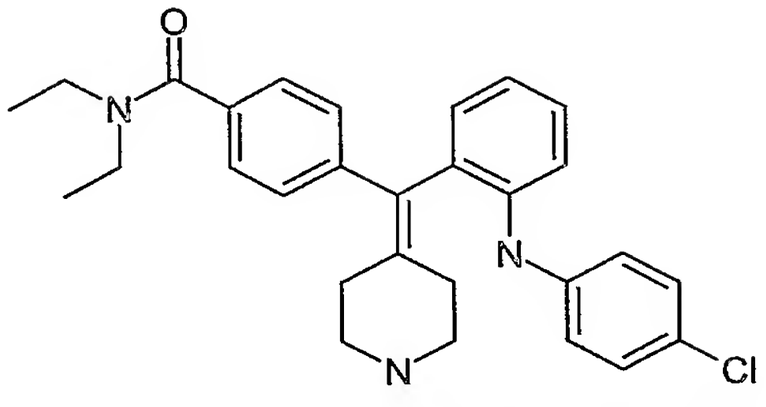
A mixture of INTERMEDIATE 6 (200 mg, 0.43 mmol), bromonaphthalene (116 mg, 0.56 mmol), $Pd_2(dba)_3$ (16 mg, 0.017 mmol), NaO^tBu (58 mg, 0.60 mmol), (±)-BINAP (21 mg, 0.034 mmol) in toluene (2.4 mL) was contained in a microwave process vial. The vial was flushed with N_2, capped and heated to 110 °C for 5 min using microwave irradiation. The resulting mixture was cooled, concentrated *in vacuo*, then purified by silica gel column chromatography, eluting with 1:1 EtOAc:Hexanes. The product was dissolved in CH_2Cl_2 (10 mL) and trifluoroacetic acid (1.3 mL) was added. The reaction was stirred overnight at room temperature then concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 20-45% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 23 (138 mg, 45% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a beige solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 1.00 (t, J=6.54 Hz, 3 H), 1.19 (t, J=6.74 Hz, 3 H), 2.54-2.75 (m, 4 H), 3.08-3.21 (m, 4 H), 3.23-3.31 (m, 2 H), 3.42-3.53 (m, 2 H), 6.78 (dd, J=8.01, 0.98 Hz, 1 H), 6.88 (dd, J=7.42, 0.98 Hz, 1 H), 6.98 (dt, J=7.47, 1.27 Hz, 1 H), 7.11-7.20 (m, 5 H), 7.23-7.33 (m, 3 H), 7.42 (dq, J=6.83, 1.17 Hz, 1 H), 7.47 (d, J=8.20 Hz, 1 H), 7.56 (d, J=8.40 Hz, 1 H), 7.80 (d, J=8.20 Hz, 1 H). Found: C, 66.35; H, 5.04; N, 6.65. $C_{33}H_{35}N_3O$ x 1.4 CF_3CO_2H has C, 66.22; H, 5.65; N, 6.47 %.

COMPOUND 24: *N,N*-diethyl-4-[{2-[(3-fluorophenyl)amino]phenyl}(piperidin-4-ylidene)methyl]benzamide



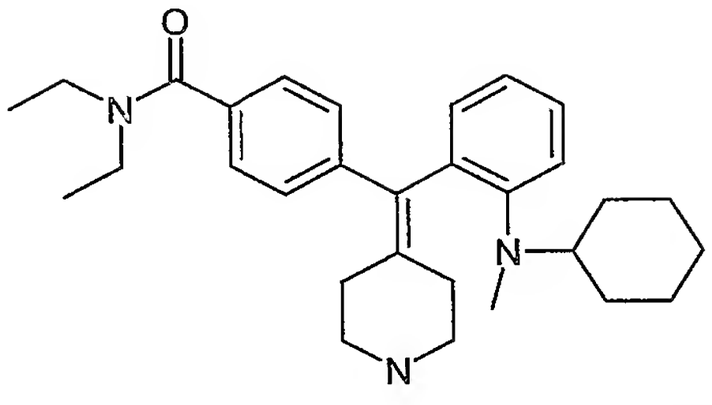
A mixture of INTERMEDIATE 6 (200 mg, 0.43 mmol), 3-fluoroiodobenzene (124 mg, 0.56 mmol), $Pd_2(dba)_3$ (16 mg, 0.017 mmol), NaO^tBu (58 mg, 0.60 mmol), (±)-BINAP (21 mg, 0.034 mmol) in toluene (2.4 mL) was contained in a microwave process vial. The vial was flushed with N_2, capped and heated to 110 °C for 25 min using microwave irradiation. The resulting mixture was cooled, concentrated *in vacuo*, then purified by silica gel column chromatography, eluting with 1:1 EtOAc:Hexanes. The product was dissolved in CH_2Cl_2 (10 mL) and trifluoroacetic acid (1.3 mL) was added. The reaction was stirred overnight at room temperature then concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 15-40% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 24 (99 mg, 34% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a light grey solid. Purity (HPLC): > 95%; ^{1}H NMR (400 MHz, CD_3OD) δ 1.00 (t, J=6.83 Hz, 3 H), 1.18 (t, J=6.83 Hz, 3 H), 2.47-2.74 (m, 4 H), 3.01 (q, J=6.83 Hz, 2 H), 3.14-3.27 (m, 4 H), 3.46 (q, J=5.86 Hz, 2 H), 6.32-6.39 (m, 2 H), 6.46-6.50 (m, 1 H), 6.97-7.05 (m, 1 H), 7.07-7.32 (m, 8 H). Found: C, 62.96; H, 5.62; N, 7.17. $C_{29}H_{32}FN_3O$ x 1.2 CF_3CO_2H x 0.2 H_2O has C, 63.07; H, 5.66; N, 7.03 %.

COMPOUND 25: 4-[{2-[(4-chlorophenyl)amino]phenyl}(piperidin-4-ylidene)methyl]-*N*,*N*-diethylbenzamide



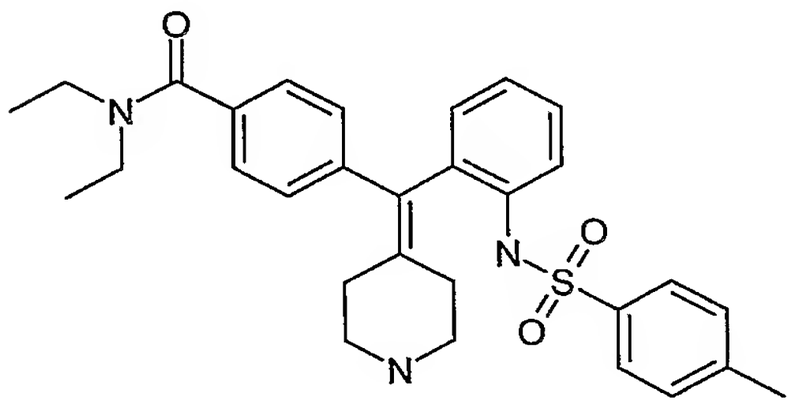
A mixture of INTERMEDIATE 6 (200 mg, 0.43 mmol), 4-bromochlorobenzene (107 mg, 0.56 mmol), $Pd_2(dba)_3$ (16 mg, 0.017 mmol), NaO^tBu (58 mg, 0.60 mmol), (±)-BINAP (21 mg, 0.034 mmol) in toluene (2.4 mL) was contained in a microwave process vial. The vial was flushed with N_2, capped and heated to 110 °C for 5 min using microwave irradiation. The resulting mixture was cooled, concentrated *in vacuo*, then purified by silica gel column chromatography, eluting with 2:3 EtOAc:Hexanes. The product was dissolved in CH_2Cl_2 (10 mL) and trifluoroacetic acid (1.3 mL) was added. The reaction was stirred overnight at room temperature then concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 20-50% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 25 (139 mg, 46% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a beige solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 1.01 (t, J=6.83 Hz, 3 H), 1.18 (t, J=6.83 Hz, 3 H), 2.46-2.75 (m, 4 H), 3.00 (q, J=6.57 Hz, 2 H), 3.15-3.30 (m, 4 H), 3.46 (q, J=6.70 Hz, 2 H), 6.64-6.69 (m, 2 H), 6.98-7.03 (m, 2 H), 7.06 (dt, J=7.37, 1.27 Hz, 1 H), 7.15-7.21 (m, 5 H), 7.23-7.28 (m, 2 H). Found: C, 60.39; H, 5.29; N, 6.65. $C_{29}H_{32}ClN_3O$ x 1.4 CF_3CO_2H has C, 60.28; H, 5.31; N, 6.63 %.

COMPOUND 26: 4-[{2-[cyclohexyl(methyl)amino]phenyl}(piperidin-4-ylidene)methyl]-*N*,*N*-diethylbenzamide



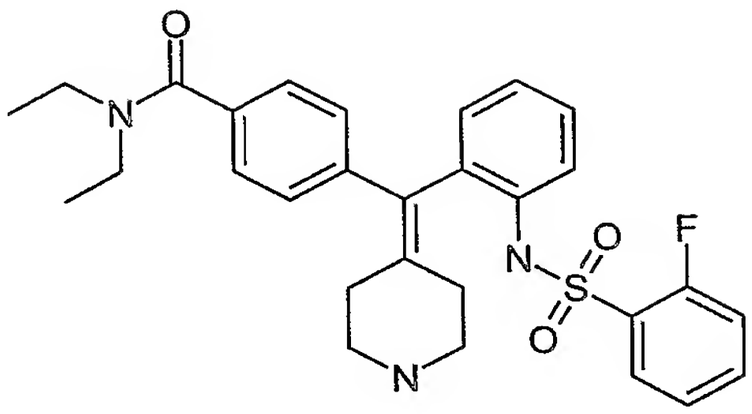
To a suspension of INTERMEDIATE 6 (175 mg, 0.38 mmol) and cyclohexanone (41 mg, 0.42 mmol) in MeOH (5 mL) was added decaborane (14 mg, 0.11 mmol). The reaction was stirred overnight at room temperature under N_2, then concentrated *in vacuo*. The residue was filtered through a short plug of silica gel eluting with 1:1 EtOAc:Hexanes and concentrated *in vacuo*. To a solution of the product (206 mg, 0.38 mmol) in MeOH (4 mL) was added formaldehyde (37% in H_2O, 0.084 mL, 1.13 mmol). The reaction was stirred for 30 minutes at room temperature. Decaborane (28 mg, 0.23 mmol) was added and the reaction was stirred for one hour at room temperature under N_2, then concentrated *in vacuo*. The residue was filtered through a short plug of silica gel eluting with 1:1 EtOAc:Hexanes and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and trifluoroacetic acid (1.2 mL) was added. The reaction was stirred overnight at room temperature, then concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 5-30% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 26 (181 mg, 70% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a coloress solid. Purity (HPLC): > 99%; ^{1}H NMR (400 MHz, CD_3OD) δ 0.95 (br s, 3 H), 1.08 (br t, J=6.35 Hz, 3 H), 1.21 (br t, J=6.44 Hz, 3 H), 1.18-1.25 (m, 2 H), 1.45-1.63 (m, 3 H), 1.70 (br s, 2 H), 2.39-2.54 (m, 2 H), 2.71-2.93 (m, 5 H), 3.02 (br s, 1 H), 3.07-3.21 (m, 2 H), 3.22-3.43 (m, 4 H), 3.51 (br q, J=6.64 Hz, 2 H), 7.35 (s, 5 H), 7.50 (br s, 3 H). Found: C, 52.62; H, 6.35; N, 5.00. $C_{30}H_{41}N_3O$ x 2.5 CF_3CO_2H x 3.0 H_2O has C, 52.63; H, 6.25; N, 5.26 %.

COMPOUND 27: *N,N*-diethyl-4-[(2-{[(4-methylphenyl)sulfonyl]amino}phenyl)(piperidin-4-ylidene)methyl]benzamide



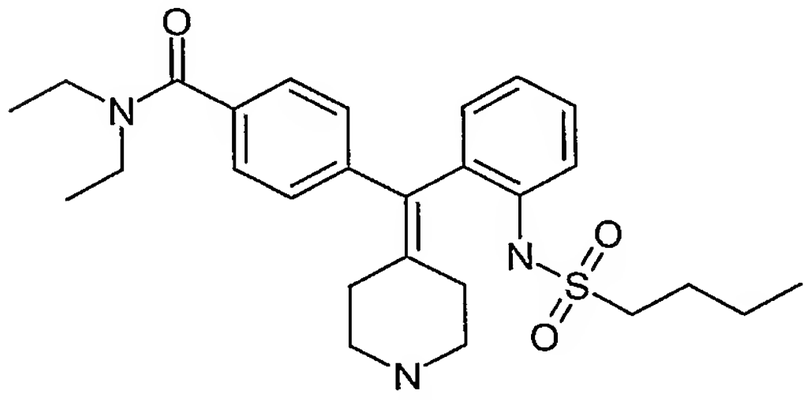
Using the same method as for COMPOUND 13 and using INTERMEDIATE 6 (175 mg, 0.38 mmol) and *p*-toluenesulfonyl chloride (144 mg, 0.76 mmol), except the residue was purified by reverse phase HPLC (gradient 15-40% CH_3CN in H_2O containing 0.1% trifluoroacetic acid), afforded COMPOUND 27 (181 mg, 76% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a beige solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 1.11 (br t, J=6.64 Hz, 3 H), 1.22 (br t, J=7.03 Hz, 3 H), 2.40 (s, 3 H), 2.42-2.51 (m, 1 H), 2.51-2.61 (m, 2 H), 2.73-2.82 (m, 1 H), 3.22-3.34 (m, 5 H), 3.39-3.47 (m, 1 H), 3.49-3.57 (m, 2 H), 6.67 (dd, J=7.81, 0.98 Hz, 1 H), 7.11 (ddd, J=7.81, 7.03, 1.95 Hz, 1 H), 7.19-7.29 (m, 4 H), 7.31 (d, J=8.20 Hz, 4 H), 7.53 (d, J=8.40 Hz, 2 H). Found: C, 57.97; H, 5.36; N, 6.31. $C_{30}H_{35}N_3O_3S$ x 1.4 CF_3CO_2H x 0.1 H_2O has C, 58.01; H, 5.43; N, 6.19 %.

COMPOUND 28: *N,N*-diethyl-4-[(2-{[(2-fluorophenyl)sulfonyl]amino}phenyl)(piperidin-4-ylidene)methyl]benzamide



Using the same method as for COMPOUND 13 and using INTERMEDIATE 6 (175 mg, 0.38 mmol) and 2-fluorobenzenesulfonyl chloride (147 mg, 0.76 mmol) afforded COMPOUND 28 (121 mg, 51% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a beige solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 1.11 (br t, J=6.64 Hz, 3 H), 1.23 (br t, J=6.83 Hz, 3 H), 2.43-2.61 (m, 3 H), 2.73-2.81 (m, 1 H), 3.22-3.35 (m, 5 H), 3.39-3.48 (m, 1 H), 3.53 (br q, J=6.96 Hz, 2 H), 6.71 (d, J=7.42 Hz, 1 H), 7.12 (ddd, J=7.91, 6.93, 2.15 Hz, 1 H), 7.23-7.33 (m, 8 H), 7.63-7.68 (m, 1 H), 7.70 (dt, J=7.03, 1.76 Hz, 1 H). Found: C, 56.89; H, 5.08; N, 6.33. $C_{29}H_{32}FN_3O_3S$ x 1.2 CF_3CO_2H x 0.2 H_2O has C, 56.96; H, 5.12; N, 6.35 %.

COMPOUND 29: 4-[{2-[(butylsulfonyl)amino]phenyl}(piperidin-4-ylidene)methyl]-*N,N*-diethylbenzamide



Using the same method as for COMPOUND 13 and using INTERMEDIATE 6 (208 mg, 0.449 mmol) and butane-1-sulfonyl chloride (0.12 mL, 0.93 mmol) afforded COMPOUND 29 (95.7 mg, 36% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a slightly off-white solid. Purity (HPLC): >

94%; ^{1}H NMR (400 MHz, CD_3OD) δ 0.91 (t, J=7.4 Hz, 3 H), 1.12 (br t, J=6.9 Hz, 3 H), 1.23 (br t, J=7.1 Hz, 3 H), 1.35-1.46 (m, 2 H), 1.65-1.74 (m, 2 H), 2.40-2.62 (m, 3 H), 2.73-2.82 (m, 1 H), 2.85-3.02 (m, 2 H), 3.18-3.42 (m, 6 H), 3.53 (br q, J=7.2 Hz, 2 H), 7.28-7.39 (m, 8 H). Found: C, 55.52; H, 5.90; N, 6.73. $C_{27}H_{37}N_3O_3S$ x 1.4 CF_3CO_2H x 0.1 H_2O has C, 55.48; H, 6.03; N, 6.51 %.

INTERMEDIATE 7: 4-[[4-[(diethylamino)carbonyl]phenyl](2-nitrophenyl)methylene]- 1-piperidinecarboxylic acid-1,1-dimethylethyl ester

To a mixture of INTERMEDIATE 5 (1000 mg, 2.22 mmol) and 2-nitrophenylboronic acid (556 mg, 3.33 mmol) in toluene (28 mL) and ethanol (6.0 mL) was added 2.0 M Na_2CO_3 (4.4 mL). Palladium tetrakistriphenylphosphine (257 mg, 0.22 mmol) was added and the resulting mixture was heated overnight at 90 °C under N_2. The reaction was then concentrated *in vacuo* and the residue was diluted with brine. The aqueous phase was extracted with EtOAc (2x). The combined organic phases was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography, eluting with 1:1 EtOAc:Hexanes, to give INTERMEDIATE 7 as a brown oil (244 mg, 22% yield). ^{1}H NMR (400MHz, $CDCl_3$) δ 1.12 (br s, 3H), 1.22 (br s, 3H), 1.45 (s, 9H), 2.07-2.15 (m, 2H), 2.26-2.36 (m, 1H), 2.41-2.50 (m, 1H), 3.20-3.43 (m, 4H), 3.45-3.62 (m, 4H), 7.22 (d, J = 8.20 Hz, 2H), 7.30 (d, J = 8.20 Hz, 3H), 7.40-7.46 (m, 1H), 7.58 (dt, J = 7.62, 1.17 Hz, 1H), 7.90 (dd, J = 8.10, 1.07 Hz, 1H).

INTERMEDIATE 8: 4-[(1-benzylpiperidin-4-ylidene)(2-nitrophenyl)methyl]-*N,N*-diethylbenzamide

To a solution of INTERMEDIATE 7 (244 mg, 0.49 mmol) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (1.3 mL). The reaction was stirred overnight at room temperature and concentrated *in vacuo*. The residue was redissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ (1x). The organic phase was collected and

the aqueous phase was extracted with CH_2Cl_2 (1x). The combined organic phases was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue and benzaldehyde (0.101 mL, 0.99 mmol) were dissolved in 1,2-dichloroethane (13 mL). Glacial acetic acid (57 μL, 0.99 mmol)) was added to the reaction followed by $NaBH(OAc)_3$ (262 mg, 1.24 mmol). The reaction was stirred overnight at room temperature, concentrated *in vacuo*, redissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ (1x). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (1x). The combined organic phases was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by filtration through a short plug of silica gel, eluting with a gradient of 100% CH_2Cl_2 to 1:9 MeOH/CH_2Cl_2, to give INTERMEDIATE 8 as a dark yellow oil (238 mg, 93% yield). ^{1}H NMR (400MHz, $CDCl_3$) δ 1.10 (br s, 3H), 1.24 (br s, 3H), 2.09-2.23 (m, 2H), 2.31-2.55 (m, 6H), 3.24 (br s, 2H), 3.46-3.57 (m, 4H), 7.20-7.34 (m, 8H), 7.36-7.43 (m, 3H), 7.55 (dt, J = 7.52, 1.37 Hz, 1H), 7.87 (dd, J = 8.20, 1.17 Hz, 1H).

INTERMEDIATE 9: 4-((2-aminophenyl){4-[(diethylamino)carbonyl]phenyl}methylene)piperidine-1-*tert*-butyl carboxylate

To a mixture of INTERMEDIATE 5 (1080 mg, 2.39 mmol) and 2-aminophenylboronic acid (426 mg, 3.11 mmol) in toluene (31 mL) and ethanol (6.2 mL) was added 2.0 M Na_2CO_3 (4.8 mL). Palladium tetrakistriphenylphosphine (276 mg, 0.24 mmol) was added and the resulting mixture was heated overnight at 90 °C under N_2. The reaction was then concentrated *in vacuo* and the residue was diluted with brine. The aqueous phase was extracted with EtOAc (2x). The combined organic phases was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography, eluting with 7:3 EtOAc:Hexanes, to give INTERMEDIATE 9 as a brown solid (1039 mg, 94% yield). ^{1}H NMR (400MHz, $CDCl_3$) δ 1.12 (br s, 3H), 1.23 (br s, 3H), 1.46 (s, 9H), 2.15-2.27 (m, 2H), 2.40-2.51 (m, 2H), 3.22-3.44 (m, 4H), 3.46-3.78 (m, 6H), 6.69 (d, J = 7.81

Hz, 1H), 6.73 (dt, J = 7.47, 1.07 Hz, 1H), 6.95 (dd, J = 7.52, 1.46 Hz, 1H), 7.09 (dt, J = 7.62, 1.56 Hz, 1H), 7.21 (d, J = 8.20 Hz, 2H), 7.31 (d, J = 8.20 Hz, 2H).

COMPOUND 31: 4-[[2-(acetylamino)phenyl](piperidin-4-ylidene)methyl]-*N*,*N*-diethylbenzamide

To a solution of INTERMEDIATE 9 (250 mg, 0.54 mmol) in CH_2Cl_2 (15 mL) was added triethylamine (225 μL, 1.62 mmol), followed by acetyl chloride (50 μL, 0.70 mmol). The reaction was stirred overnight at room temperature, diluted with CH_2Cl_2, and washed with saturated aqueous $NaHCO_3$ (1x). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (1x). The combined organic phases was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (15 mL) and trifluoracetic acid (1.7 mL) was added. The reaction was stirred for 4 hours at room temperature and concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 5-30% CH_3CN in H_2O containing 0.1% trifluoroacetic acid). The product was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ (1x). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (1x). The combined organic phases was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give COMPOUND 31 as a colorless solid (133 mg, 61% yield). ^{1}H NMR (400MHz, $CDCl_3$) δ 1.11 (br s, 3H), 1.23 (br s, 3H), 2.07 (s, 3H), 2.09-2.25 (m, 2H), 2.51 (br t, J = 5.47 Hz, 2H), 2.90 (t, J = 5.57 Hz, 2H), 2.96 (br t, J = 5.47 Hz, 2H), 3.26 (br s, 2H), 3.53 (br s, 2H), 7.06-7.13 (m, 2H), 7.15 (d, J = 8.20 Hz, 2H), 7.27-7.35 (m, 4H), 8.22 (d, J = 8.40 Hz, 1H).

COMPOUND 32: methyl 2-[{4-[(diethylamino)carbonyl]phenyl}(piperidin-4-ylidene)methyl]phenylcarbamate

A mixture of zinc dust (39 mg, 0.59 mmol) and methyl chloroformate (46 μL, 0.59 mmol) in toluene (2 mL) was stirred for 1 hour at room temperature. A solution of INTEMEDIATE 9 (250 mg, 0.54 mmol) in toluene (4 mL) was added to the

reaction dropwise. The reaction was stirred overnight at room temperature, diluted with CH_2Cl_2, filtered and then washed with 1N $NaHCO_3$ (1x). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (1x). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography eluting with 3:1 EtOAc:Hexanes. The product was dissoved in CH_2Cl_2 (15 mL) and trifluoroacetic acid (1.7 mL) was added. The reaction was stirred ovenight at room temperature and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ (1x). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (1x). The combined organic phases was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give COMPOUND 32 as a dark yellow oil (88 mg, 36% yield). ^{1}H NMR (400MHz, $CDCl_3$) δ 1.11 (br s, 3H), 1.23 (br s, 3H), 2.11-2.22 (m, 2H), 2.50 (t, J = 5.66 Hz, 2H), 2.94 (dq, J = 24.85, 4.93 Hz, 4H), 3.26 (br s, 2H), 3.53 (br s, 2H), 3.74 (s, 3H), 6.84 (br s, 1H), 7.01-7.07 (m, 2H), 7.15 (d, J = 8.40 Hz, 2H), 7.27-7.33 (m, 4H), 8.07 (d, J = 7.42 Hz, 1H).

INTERMEDIATE 10: *N,N*-diethyl-4-[(2-nitrophenyl)(piperidin-4-ylidene)methyl]benzamide

To a mixture of INTERMEDIATE 5 (5.16 g, 11.7 mmol) and 2-nitrophenylboronic acid (2.93 g, 17.5 mmol) in toluene (125 mL) and ethanol (25 mL) was added 2.0 M Na_2CO_3 (14.6 mL). Palladium tetrakistriphenylphosphine (1.35 g, 1.17 mmol) was added and the resulting mixture was heated overnight at 90 °C under N_2. The reaction was then concentrated *in vacuo* and the residue was diluted with brine. The aqueous phase was extracted with two portions of EtOAc. The combined organic phases was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography, eluting with 1:1 EtOAc:Hexanes. The material was dissolved in dichloromethane (20 mL) and trifluroacetic acid (5 mL) was added. The reaction was stirred overnight at room

temperature and saturated aqueous sodium bicarbonate was added. The phases were separated and the aqueous phase was extracted with two portions of dichloromethane. The combined organic phases was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give INTERMEDIATE 10 as a brown solid (1.50 g, 30%). ^{1}H NMR (400MHz, $CDCl_3$) δ 1.06-1.16 (m, 3H), 1.18-1.29 (m, 3H), 2.29-2.39 (m, 1H), 2.42-2.53 (m, 1H), 2.54-2.73 (m, 2H), 2.99-3.10 (m, 2H), 3.16-3.29 (m, 4H), 3.47-3.59 (m, 2H), 7.20 (d, J = 8.40 Hz, 2H), 7.29-7.33 (m, 3H), 7.47 (ddd, J = 8.20, 7.62, 1.56 Hz, 1H), 7.61 (td, J = 7.62, 1.37 Hz, 1H), 7.92 (dd, J = 8.20, 1.17 Hz, 1H).

INTERMEDIATE 11: 4-[bromo(1-butylpiperidin-4-ylidene)methyl]-*N*,*N*-diethyl benzamide

To INTERMEDIATE 5 (5000 mg, 11.08 mmol) in CH_2Cl_2 (100 mL) was added TFA (15 mL) at rt. The resulting mixture was stirred at rt for 4 hrs under N_2. The reaction was then concentrated *in vacuo* and the residue was diluted with sat. $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (2x). The combined organic phases was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. To this crude product in dichloroethane (50 mL) was added butyraldehyde (878 mg, 12.2 mmol) followed by $NaBH(OAc)_3$ (3520 mg, 16.62 mmol) at rt under nitrogen protection. The reaction was stirred overnight at room temperature, concentrated *in vacuo*, redissolved in CH_2Cl_2 and washed with 2M NaOH solution (1x). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (2x). The combined organic phases was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with a gradient of 9:1 CH_2Cl_2/EtOAc to 3:2 CH_2Cl_2/EtOAc to give INTERMEDIATE 11 as a pale yellow oil (1807 mg, 40% yield). ^{1}H NMR (400MHz, $CDCl_3$) δ 0.92 (t, J = 7.32 Hz, 3H), 1.07-1.19 (m, 3H), 1.20-1.39 (m, 4H), 1.42-1.54 (m, 2H), 1.57-1.64 (m, 1H), 2.24-2.39 (m, 6H), 2.55 (t, J = 5.86 Hz, 2H), 2.70 (t, J = 8.00 Hz, 2H), 3.23-3.36 (m, 2H), 3.48-3.62 (m, 2H), 7.31 (d, J = 8.00 Hz, 2H) 7.35 (d, J = 8.00, 2H).

INTERMEDIATE 12: 4-{bromo[1-(pyridin-4-ylmethyl)piperidin-4-ylidene]methyl}-*N,N*-diethylbenzamide

Using the same method as for INTERMEDIATE 11 and using INTERMEDIATE 5 (6000 mg, 13.3 mmol) and 4-pyridinecarboxaldehyde (3242 mg, 9.24 mmol) afforded INTERMEDIATE 12 (3675 mg, 90% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 1.12 (t, J = 6.83 Hz, 3H), 1.23 (t, J = 6.93 Hz, 3H), 2.27-2.33 (m, 2H), 2.38-2.43 (m, 2H), 2.57 (t, J = 5.76 Hz, 2H), 2.69-2.75 (m, 2H), 3.24-3.34 (m, 3H), 3.53 (q, J = 7.23 Hz, 1H), 3.59 (s, 2H), 7.36 (s, 4H), 7.42-7.46 (m, 2H), 8.43-8.47 (m, 2H).

INTERMEDIATE 13: 4-{bromo[1-(pyridin-3-ylmethyl)piperidin-4-ylidene]methyl}-*N,N*-diethylbenzamide

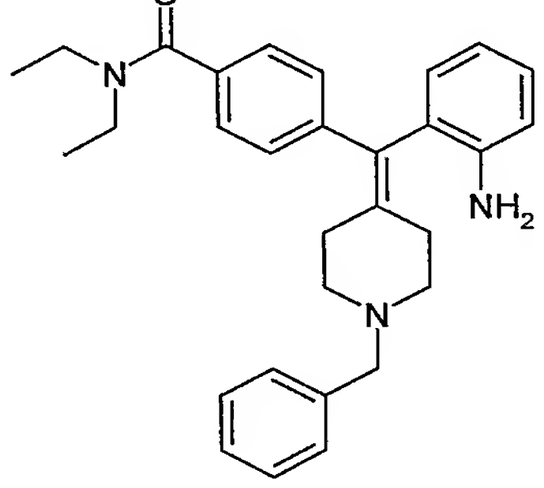
Using the same method as for INTERMEDIATE 11 and using INTERMEDIATE 5 (4000 mg, 8.87 mmol) and 3-pyridinecarboxaldehyde (531.3 mg, 4.96 mmol) afforded INTERMEDIATE 13 (2050 mg, 93% yield) as a light green oil. ^{1}H NMR (400 MHz, CD_3OD) δ 1.12 (t, J = 7.23 Hz, 3H), 1.23 (t, J = 7.23 Hz, 3H), 2.25-2.31 (m, 2H), 2.37-2.44 (m, 2H), 2.57 (t, J = 5.76 Hz, 2H), 2.67-2.74 (m, 2H), 3.24-3.34 (m, 3H), 3.48-3.57 (m, 1H), 3.59 (s, 2H), 7.36 (s, 4H), 7.38-7.43 (m, 1H), 7.80-7.87 (m, 1H), 8.43 (dd, J = 4.88, 1.56 Hz, 1H), 8.49 (d, J = 1.56 Hz, 1H).

INTERMEDIATE 14: 4-{bromo[1-(pyridin-2-ylmethyl)piperidin-4-ylidene]methyl}-*N,N*-diethylbenzamide

Using the same method as for INTERMEDIATE 11 and using INTERMEDIATE 5 (5000 mg, 11.0 mmol) and 2-pyridinecarboxaldehyde (1140 mg, 10.7 mmol) afforded INTERMEDIATE 14 (4096 mg, 87% yield) as pale yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 1.12 (t, J = 6.93 Hz, 3H), 1.23 (t, J = 7.03 Hz, 3H), 2.26-2.32 (m,

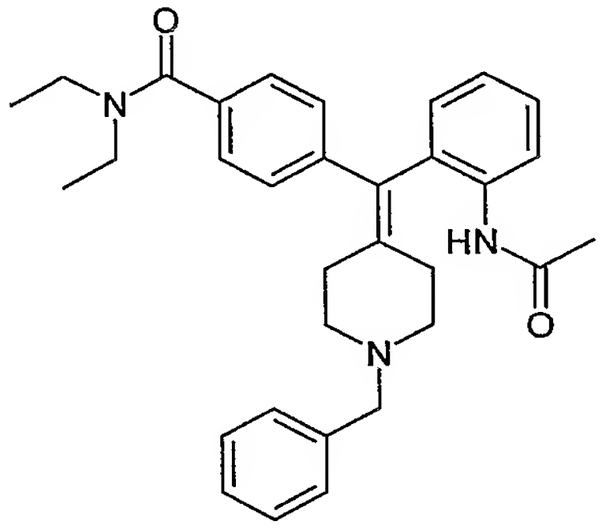
2H), 2.40-2.46 (m, 2H), 2.60 (t, J = 5.66 Hz, 2H), 2.67-2.75 (m, 2H), 3.24-3.35 (m, 3H), 3.53 (q, J = 6.96 Hz, 1H), 3.66 (s, 2H), 7.28-7.33 (m, 1H), 7.36 (s, 4H), 7.54 (d, J = 7.81 Hz, 1H), 7.78-7.84 (m, 1H), 8.44-8.48 (m, 1H).

COMPOUND 30: 4-[(2-aminophenyl)(1-benzylpiperidin-4-ylidene)methyl]-*N*,*N*-diethylbenzamide



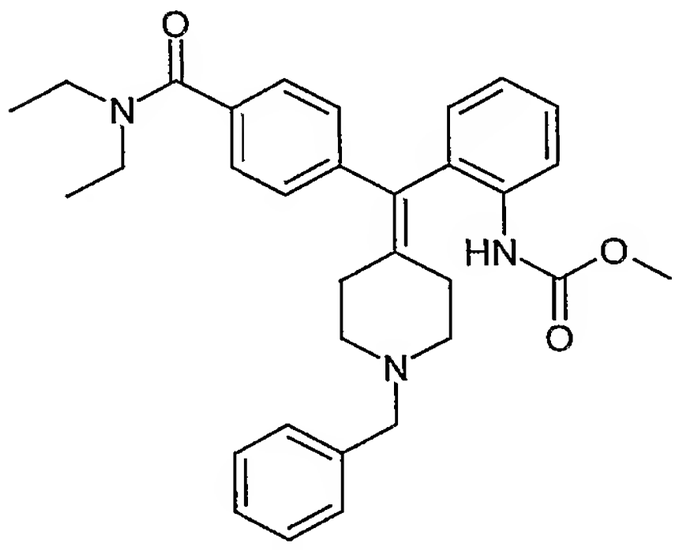
To a solution of INTERMEDIATE 8 (238 mg, 0.49 mmol) in 4:2:1:1 of $EtOH/THF/H_2O/NH_4Cl_{(aq)}$ was added iron powder (275 mg, 4.92 mmol). The reaction was microwaved at 140 °C for 10 min and then filtered through celite. The celite was rinsed with EtOAc. The filtrate was concentrated *in vacuo*, redissolved in EtOAc, and washed with saturated aqueous $NaHCO_3$ (1x) and brine (1x). The organic phase was collected and the aqueous phases were extracted with EtOAc (1x). The combined organic phases was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 10-40% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 30 (118 mg, 35% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a beige solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 1.09 (br t, J = 6.64 Hz, 3H), 1.21 (br t, J = 6.83 Hz, 3H), 2.30-2.63 (m, 3H), 2.84-2.96 (m, 1H), 3.00-3.32 (m, 4H), 3.51 (br q, J = 6.77 Hz, 4H), 4.32 (s, 2H), 6.70 (s, 1H), 6.80-6.89 (m, 2H), 7.03-7.19 (m, 1H), 7.31 (s, 4 H) 7.48 (s, 5 H). Found: C, 60.57; H, 6.01; N, 6.60. $C_{30}H_{35}N_3O$ x 1.5 CF_3CO_2H x 1.6 H_2O has C, 60.65; H, 6.12; N, 6.43 %.

COMPOUND 33: 4-[[2-(acetylamino)phenyl](1-benzylpiperidin-4-ylidene)methyl]-*N,N*-diethylbenzamide



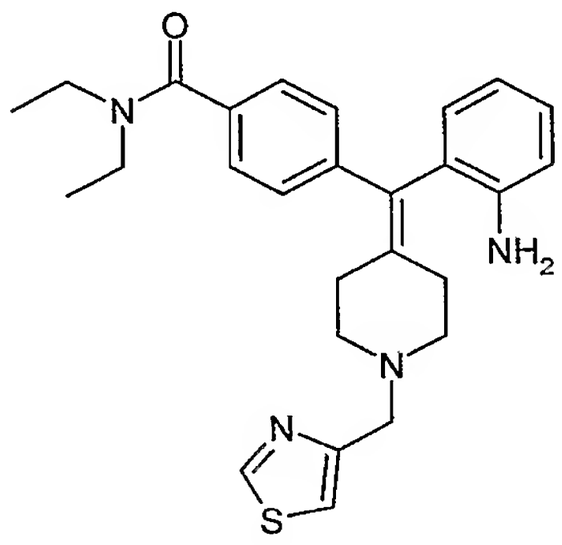
To a solution of COMPOUND 31 (133 mg, 0.33 mmol) and benzaldehyde in 1,2-dichoroethane (9 mL) was added glacial acetic acid (38 μL, 0.66 mmol), followed by $NaBH(OAc)_3$ (174 mg, 0.82 mmol). The reaction was stirred overnight at room temperature, concentrated *in vacuo*, redissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ (1x). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (2x). The combined organic phases was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 10-40% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 33 (127 mg, 64% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 1.09 (br s, 3H), 1.20 (t, J = 6.64 Hz, 3H), 1.89 (d, J = 17.18 Hz, 3H), 2.30-2.54 (m, 1H), 2.55-2.72 (m, 1H), 2.83-3.09 (m, 1H), 3.10-3.30 (m, 5H), 3.43-3.63 (m, 4H), 4.34 (d, J = 13.28 Hz, 2H), 7.11 (d, J = 7.62 Hz, 1H), 7.17 (d, J = 7.62 Hz, 1H), 7.25-7.39 (m, 6H), 7.45-7.54 (m, 5H). Found: C, 61.21; H, 5.68; N, 6.00. $C_{32}H_{37}N_3O_2$ x 1.7 CF_3CO_2H x 0.3 H_2O has C, 61.19; H, 5.70; N, 6.05 %.

COMPOUND 34: methyl 2-((1-benzylpiperidin-4-ylidene){4-[(diethylamino)carbonyl]phenyl}methyl)phenylcarbamate



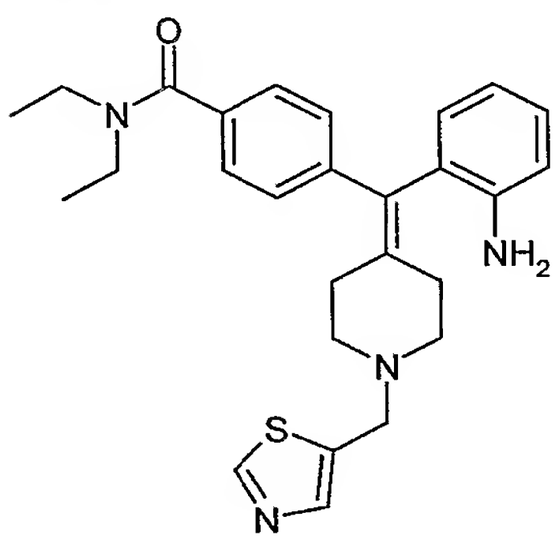
Using the same method as for COMPOUND 33 and using COMPOUND 32 (88 mg, 0.21 mmol) and benzaldehyde (44 mg, 0.42 mmol) afforded COMPOUND 34 (81 mg, 62% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 1.08 (br t, J = 6.93 Hz, 3H), 1.20 (br t, J = 6.83 Hz, 3H), 2.36-2.64 (m, 3H), 2.81-3.00 (m, 1H), 3.00-3.18 (m, 2H), 3.20-3.30 (m, 2H), 3.45-3.55 (m, 4H), 3.57 (s, 3H), 4.33 (br d, J = 7.03 Hz, 2H), 7.14-7.24 (m, 4H), 7.26-7.40 (m, 4H), 7.48 (s, 5H). Found: C, 60.84; H, 5.67; N, 6.17. $C_{32}H_{37}N_3O_3$ x 1.5 CF_3CO_2H x 0.4 H_2O has C, 60.93; H, 5.74; N, 6.09 %.

COMPOUND 35: 4-{(2-aminophenyl)[1-(1,3-thiazol-4-ylmethyl)piperidin-4-ylidene]methyl}-N,N-diethylbenzamide



A solution of INTERMEDIATE 10 (0.760 g, 1.93 mmol), 4-chloromethylthiazole hydrochloride (0.493 g, 2.90 mmol) and potassium carbonate (0.533 g, 3.86 mmol) in dry DMF (20 mL) was stirred for 18 h at room temperature under N_2. The mixture was concentrated *in vacuo*, then diluted with dichloromethane. The solution was washed with one portion of saturated aqueous sodium bicarbonate and one portion of brine. The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was dissolved in a 4:2:1:1 mixture of ethanol/THF/H_2O/$NH_4Cl_{(aq)}$ (4 mL) in a microwaveable vial. Iron powder (1.08 g, 19.3 mmol) was added and the reaction was heated in a microwave at 150 °C for 20 min and then filtered through celite. The celite was rinsed with ethyl acetate and the filtrate was concentrated. The residue was purified by flash chromatography, eluting 1% to 5% methanol in dichloromethane to give the product as a yellow solid (0.321 g, 36%). Some of the product (115 mg, 0.249 mmol) was purified by reverse phase HPLC (gradient 10-45% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 35 (89 mg, 19% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a yellow solid. HPLC Purity: >95% (215nm); >93% (254nm); >99% (280nm); ^{1}H NMR (400 MHz, CD_3OD) δ 1.11 (br t, J = 6.44 Hz, 3H), 1.23 (br t, J = 7.42 Hz, 3H), 2.47-2.59 (m, 2H), 2.64-2.76 (m, 1H), 2.84-2.98 (m, 1H), 3.24-3.33 (m, 4H), 3.48-3.59 (m, 4H), 4.53 (s, 2H), 6.86-6.97 (m, 2H), 7.10-7.21 (m, 2H), 7.30-7.37 (m, 4H), 7.85 (d, J = 1.95 Hz, 1H), 9.11 (d, J = 1.95 Hz, 1H). Found: C, 52.11; H, 5.21; N, 7.66. $C_{27}H_{32}N_4OS$ x 2.1 CF_3CO_2H x 1.1 H_2O has C, 52.05; H, 5.08; N, 7.78%.

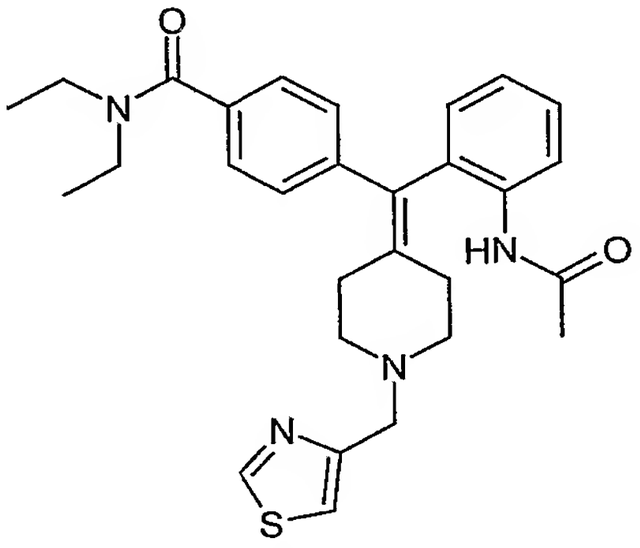
COMPOUND 36: 4-{(2-aminophenyl)[1-(1,3-thiazol-5-ylmethyl)piperidin-4-ylidene]methyl}-N,N-diethylbenzamide



To a solution of INTERMEDIATE 10 (0.717 mg, 1.82 mmol) and thiazole-5-carboxaldehyde (0.717 g, 1.82 mmol) in 1,2-dichoroethane (40 mL) was added $NaBH(OAc)_3$ (0.656 mg, 3.09 mmol). The reaction was stirred overnight at room temperature and then washed with saturated aqueous $NaHCO_3$ (1x). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (2x). The combined organic phases was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was dissolved in a 4:2:1:1 mixture of ethanol/THF/H_2O/$NH_4Cl_{(aq)}$ (4 mL) in a microwaveable vial. Iron powder (1.08 g, 19.3 mmol) was added and the reaction was heated in a microwave for at 150 °C for 20 min and then filtered through celite. The celite was rinsed with ethyl acetate and the filtrate was concentrated. The residue was purified by flash chromatography, eluting 1% to 5% methanol in dichloromethane to give the product as an orange solid (0.503 g, 64%). Some of the product (150 mg, 0.326 mmol) was purified by reverse phase HPLC (gradient 10-45% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 36 (108 mg, 30% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a yellow solid. HPLC Purity: >97% (215nm); >94% (254nm); >99% (280nm); ^{1}H NMR (400 MHz, CD_3OD) δ 1.11 (br t, J = 7.03 Hz, 3H), 1.22 (br t, J = 7.03 Hz, 3H), 2.41-2.59 (m, 2H), 2.63-2.88 (m, 2H), 3.24-3.33 (m, 4H), 3.33-3.48 (m, 2H), 3.48-3.57 (m, 2H), 4.71 (s, 2H), 6.72-6.79 (m, 1H), 6.83 (dd, J = 8.01, 0.78 Hz, 1H), 6.91-7.01 (m, 1H), 7.10 (td, J = 7.62, 1.37 Hz, 1H), 7.32-7.35 (m, 4H), 8.08 (s,

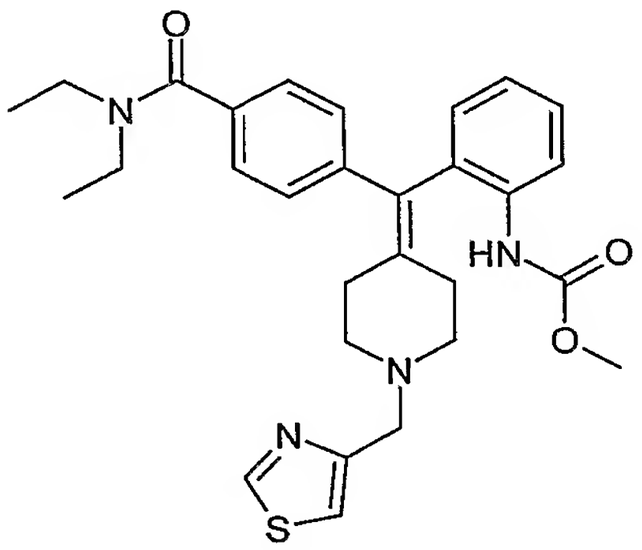
1H), 9.20 (s, 1H). Found: C, 51.64; H, 5.14; N, 7.67. $C_{27}H_{32}N_4O_2$ x 2.1 CF_3CO_2H x 1.4 H_2O has C, 51.67; H, 5.13; N, 7.72%.

COMPOUND 37: 4-{[2-(acetylamino)phenyl][1-(1,3-thiazol-4-ylmethyl)piperidin-4-ylidene]methyl}-N,N-diethylbenzamide



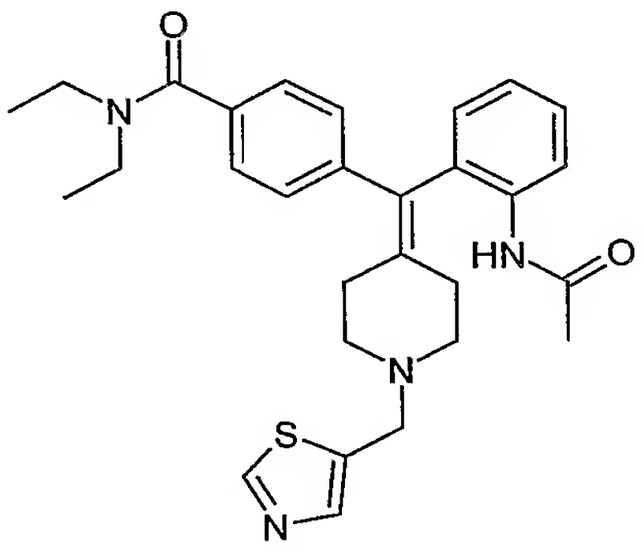
A solution of COMPOUND 35 as its free base (103 mg, 0.224 mmol), acetyl chloride (32 μL, 0.448 mmol) and triethylamine (110 μL, 0.726 mmol) in dichloromethane (10 mL) was stirred overnight at room temperature. The solution was diluted with CH_2Cl_2, and washed with saturated aqueous $NaHCO_3$ (1x). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (2x). The combined organic phases was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by reverse phase HPLC (gradient 10-45% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 37 (80 mg, 58% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a yellow solid. Purity: >97% (215nm); >94% (254nm); >99% (280nm); ^1H NMR (400 MHz, CD_3OD) δ 1.11 (br t, J = 6.64 Hz, 3H), 1.23 (br t, J = 6.64 Hz, 3H), 1.92 (s, 3H), 2.36-2.61 (m, 2H), 2.63-2.74 (m, 2H), 3.21-3.32 (m, 6H), 3.48-3.57 (m, 2H), 4.55 (s, 2H), 7.11-7.23 (m, 2H), 7.28-7.39 (m, 6H), 7.86 (s, 1H), 9.12 (d, J = 1.76 Hz, 1H). Found: C, 54.55; H, 5.48; N, 7.91. $C_{29}H_{34}N_4O_2S$ x 1.6 CF_3CO_2H x 1.3 H_2O has C, 54.59; H, 5.43; N, 7.91%.

COMPOUND 38: methyl 2-{{4-[(diethylamino)carbonyl]phenyl}[1-(1,3-thiazol-4-ylmethyl)piperidin-4-ylidene]methyl}phenylcarbamate



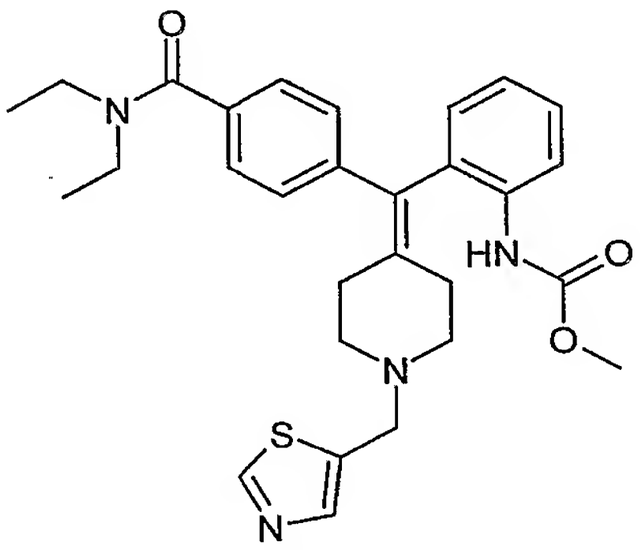
A mixture of zinc powder (15 mg, 0.22 mmol) and methyl chloroformate (17 μL, 0.22 mmol) in toluene (10 mL) was stirred for 10 min at room temperature. A solution of COMPOUND 35 (103 mg, 0.22 mmol) in toluene (5 mL) was added to the reaction dropwise. The reaction was stirred overnight at room temperature, diluted with CH_2Cl_2, and washed with saturated aqueous $NaHCO_3$ (1x). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (2x). The combined organic phases was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 10-45% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 38 (26 mg, 18% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a yellow solid. Purity: >87% (215nm); >81% (254nm); >86% (280nm); ^1H NMR (400 MHz, CD_3OD) δ 1.11 (br t, J = 6.64 Hz, 3H), 1.23 (br t, J = 6.64 Hz, 3H), 2.38-2.60 (m, 2H), 2.63-2.73 (m, 2H), 3.21-3.30 (m, 6H), 3.50-3.56 (m, 2H), 3.60 (s, 3H), 4.56 (s, 2H), 7.11-7.23 (m, 2H), 7.29-7.39 (m, 6H), 7.86 (s, 1H), 9.11 (d, J = 1.76 Hz, 1H). Found: C, 54.55; H, 5.48; N, 7.91. $C_{29}H_{34}N_4O_2S$ x 1.6 CF_3CO_2H x 1.3 H_2O has C, 54.59; H, 5.43; N, 7.91%.

COMPOUND 39: 4-{[2-(acetylamino)phenyl][1-(1,3-thiazol-5-ylmethyl)piperidin-4-ylidene]methyl}-N,N-diethylbenzamide



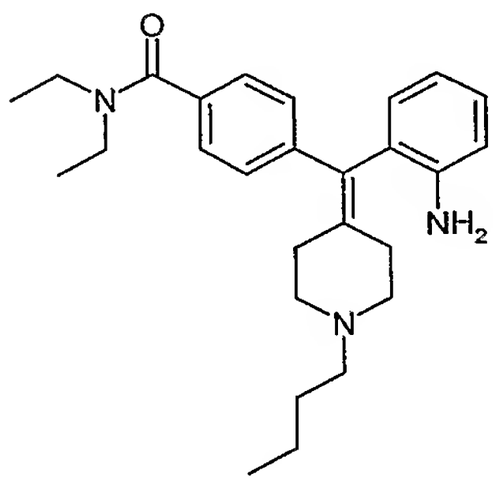
To a solution of COMPOUND 31 (0.289 g, 0.713 mmol) and thiazole-5-carboxaldehyde (0.129 g, 1.14 mmol) in 1,2-dichoroethane (20 mL) was added $NaBH(OAc)_3$ (0.257 g, 1.21 mmol). The reaction was stirred overnight at room temperature and washed with saturated aqueous $NaHCO_3$ (1x). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (2x). The combined organic phases was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 10-45% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 39 (187 mg, 43% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a white solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 1.11 (br t, J = 7.03 Hz, 3H), 1.23 (br t, J = 6.64 Hz, 3H), 1.92 (s, 3H), 2.50-2.73 (m, 4H), 3.22-3.32 (m, 5H), 3.45-3.58 (m, 3H), 4.74 (s, 2H), 7.13-7.19 (m, 2H), 7.20-7.28 (m, 1H), 7.31 (d, J = 8.40 Hz, 2H), 7.32-7.38 (m, 3H), 8.09-8.11 (m, 1H), 9.19-9.21 (m, 1H). Found: C, 53.46; H, 5.22; N, 7.30. $C_{29}H_{34}N_4O_2S$ x 1.9 CF_3CO_2H x 1.0 H_2O has C, 53.43; H, 5.18; N, 7.60%.

COMPOUND 40: methyl 2-{{4-[(diethylamino)carbonyl]phenyl}[1-(1,3-thiazol-5-ylmethyl)piperidin-4-ylidene]methyl}phenylcarbamate



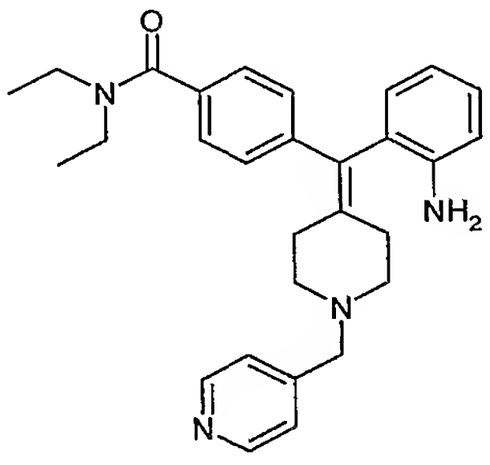
Using the same method as for COMPOUND 39 and using COMPOUND 32 (0.172 g, 0.408 mmol) and thiazole-5-carboxaldehyde (74 mg, 0.65 mmol) afforded COMPOUND 40 (0.239 mg, 93% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce an off-white solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 1.11 (br t, J = 6.25 Hz, 3H), 1.23 (br t, J = 7.03 Hz, 3H), 2.51-2.62 (m, 2H), 2.63-3.08 (m, 2H), 3.20-3.35 (m, 5H), 3.46-3.57 (m, 3H), 3.60 (s, 3H), 4.73 (s, 2H), 7.18-7.27 (m, 4H), 7.27-7.36 (m, 3H), 7.38-7.49 (m, 1H), 8.07-8.14 (m, 1H), 9.18-9.23 (m, 1H). Found: C, 52.95; H, 5.28; N, 7.48. $C_{29}H_{34}N_4O_3S$ x 1.7 CF_3CO_2H x 1.3 H_2O has C, 52.88; H, 5.25; N, 7.61%.

COMPOUND 41: 4-[(2-aminophenyl)(1-butylpiperidin-4-ylidene)methyl]-N,N-diethyl benzamide



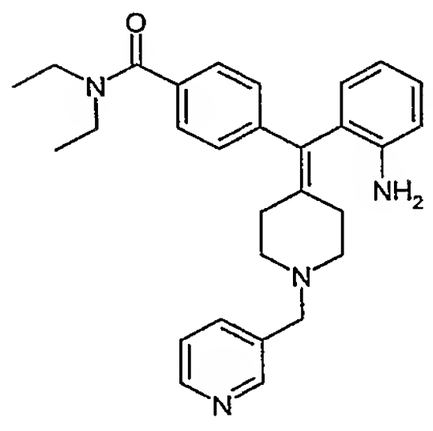
To a mixture of INTERMEDIATE 11 (1.80 g, 4.44 mmol) and 2-aminophenylboronic acid (792 mg, 5.78 mmol) in toluene (60 mL) and ethanol (13 mL) was added 2.0 M Na_2CO_3 (10 mL). Palladium tetrakistriphenylphosphine (514 mg, 0.445 mmol) was added and the resulting mixture was heated overnight at 90 °C using a pressure vessle. The reaction was then concentrated *in vacuo* and the residue was diluted with brine. The aqueous phase was extracted with EtOAc (2X). The combined organic phases was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography, eluting with a gradient of 3:2 EtOAc/ CH_2Cl_2 to 100% EtOAc to give COMPOUND 41 as a pale yellow oil (1769 mg, 95% yield). The oil (200 mg) was re-purified by reverse phase HPLC (gradient 10-70% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 41 (130 mg) as its TFA salt. This material was lyophilized from H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400MHz, $CDCl_3$) δ 0.98 (t, J = 7.03 Hz, 3H), 1.04-1.16 (m, 3H), 1.17-1.30 (m, 3H), 1.33-1.51 (m, 2H), 1.61-1.82 (m, 2H), 2.29-2.72 (m, 2H), 2.83-3.07 (m, 2H), 3.07-3.22 (m, 3H), 3.23-3.39 (m, 3H), 3.42-3.71 (m, 4H), 6.79-7.05 (m, 2H), 7.08-7.27 (m, 2H), 7.33 (s, 4H). Found: C, 58.08; H, 6.05; N, 6.63. $C_{27}H_{37}N_3O$ x 1.90 $C_2HO_2F_3$ has C, 58.14; H, 6.16; N, 6.60%

COMPOUND 42: 4-{(2-aminophenyl)[1-(pyridin-4-ylmethyl)piperidin-4-ylidene]methyl}-N,N-diethylbenzamide



Using the same method as for COMPOUND 41 and using INTERMEDIATE 12 (1.31 g, 2.95 mmol), 2-aminophenylboronic acid (526 mg, 3.84 mmol), palladium tetrakistriphenylphosphine (341 mg, 0.295 mmol), toluene (30 mL), ethanol (6 mL) and 2.0 M Na_2CO_3 (5 mL) afforded COMPOUND 42. The crude product was purified by silica gel column chromatography, eluting with EtOAc to give COMPOUND 42 as a pale yellow solid (1.32 g, 98% yield). The solid (400 mg) was re-purified by reverse phase HPLC (gradient 10-60% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 42 (456.7 mg) as its TFA salt. This material was lyophilized from H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400MHz, $CDCl_3$) δ 0.96-1.36 (m, 6H), 2.33-2.63 (m, 2H), 2.67-2.91 (m, 2H), 3.15-3.63 (m, 10H), 4.44 (s, 2H), 6.88-7.00 (m, 2H), 7.08 (d, J = 7.22 Hz, 1H), 7.14-7.23 (m, 1H), 7.26-7.40 (m, 4H), 7.74 (d, J = 2.93 Hz, 2H), 8.77 (s, 2H). Found: C, 55.54; H, 5.05; N, 7.81. $C_{29}H_{34}N_4O$ x 2.4 $C_2HO_2F_3$ x 0.1 H_2O has C, 55.61; H, 5.05; N, 7.67%

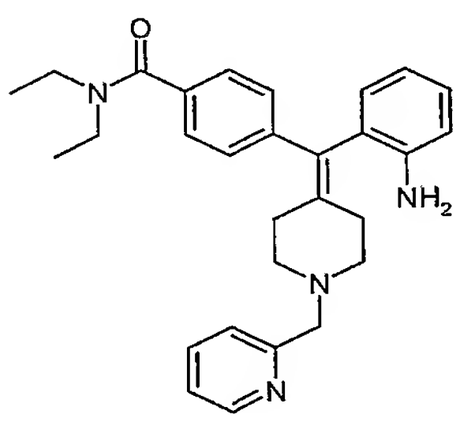
COMPOUND 43: 4-{(2-aminophenyl)[1-(pyridin-3-ylmethyl)piperidin-4-ylidene]methyl}-N,N-diethylbenzamide



Using the same method as for COMPOUND 41 and using INTERMEDIATE 13 (2.05 g, 4.64 mmol), 2-aminophenylboronic acid (826 mg, 6.03 mmol), palladium tetrakistriphenylphosphine (536 mg, 0.464 mmol), toluene (60 mL), ethanol (12 mL) and 2.0 M Na_2CO_3 (10 mL) afforded COMPOUND 43. The crude product was purified by silica gel column chromatography, eluting with EtOAc to give

COMPOUND 43 as a pale yellow solid (1.79 g, 85% yield). This solid (400 mg) was re-purified by reverse phase HPLC (gradient 10-60% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 43 as its TFA salt. This material was lyophilized from H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400MHz, $CDCl_3$) δ 0.96-1.33 (m, 6H), 2.36-2.61 (m, 2H), 2.65-2.92 (m, 2H), 3.16-3.66 (m, 10H), 4.35-4.55 (s, 2H), 6.99 (d, J = 8.20 Hz, 2H), 7.11 (d, J = 6.44 Hz, 1H), 7.21 (t, J = 7.71 Hz, 1H), 7.28-7.39 (m, 4H), 7.67 (dd, J = 7.71, 5.17 Hz, 1H), 8.15 (d, J = 8.01 Hz, 1H), 8.74 (d, J = 23.43 Hz, 2H). Found: C, 55.94; H, 5.11; N, 7.91. $C_{29}H_{34}N_4O$ x 2.3 $C_2HO_2F_3$ x 0.2 H_2O has C, 56.01; H, 5.13; N, 7.78%

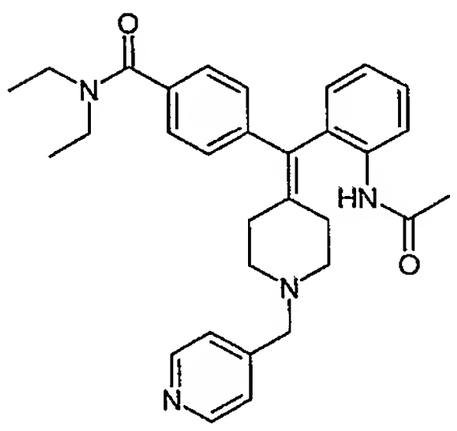
COMPOUND 44: 4-{(2-aminophenyl)[1-(pyridin-2-ylmethyl)piperidin-4-ylidene]methyl}-N,N-diethylbenzamide



Using the same method as for COMPOUND 41 and using INTERMEDIATE 14 (4.08 g, 9.27 mmol), 2-aminophenylboronic acid (1.65 g, 12.0 mmol), palladium tetrakistriphenylphosphine (1.07 g, 0.927 mmol), toluene (120 mL), ethanol (24 mL) and 2.0 M Na_2CO_3 (20 mL). The crude product was purified by flash column chromatography, eluting with EtOAc to give COMPOUND 44 as a dark yellow solid (3.10 g, 74% yield). This solid (500 mg) was re-purified by reverse phase HPLC (gradient 10-70% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 44 (487 mg) as its TFA salt. This material was lyophilized from H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400MHz, $CDCl_3$) δ 0.97-1.39 (m, 6H), 2.40-2.65 (m, 2H), 2.69-2.91 (m, 2H), 3.16-3.64 (m, 10H), 4.38-

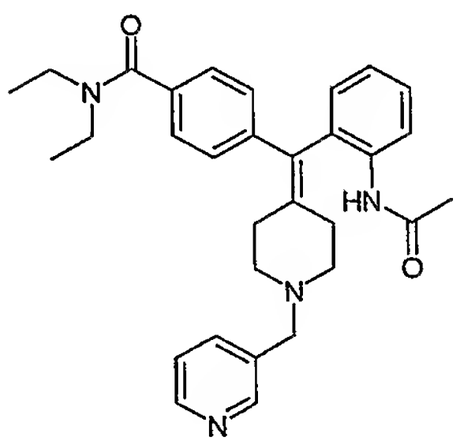
4.57 (m, 2H), 6.70-6.91 (m, 2H), 6.98 (t, J = 6.93 Hz, 1H), 7.06-7.19 (m, 1H), 7.28-7.38 (m, 4H), 7.39-7.54 (m, 2H), 7.81-7.97 (m, 1H), 8.58-8.74 (m, 1H). Found: C, 58.75; H, 5.36; N, 8.62. $C_{29}H_{35}N_4O$ x 1.8 $C_2HO_2F_3$ x 0.3 H_2O has C, 58.86; H, 5.52; N, 8.42%

COMPOUND 45: 4-{[2-(acetylamino)phenyl][1-(pyridin-4-ylmethyl)piperidin-4-ylidene]methyl}-N,N-diethylbenzamide



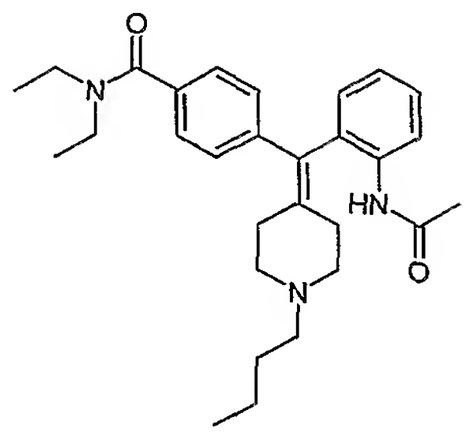
Using the same method as for COMPOUND 41 and using INTERMEDIATE 12 (590 mg, 1.33 mmol), 2-(acetylaminophenyl)boronic acid (310.6 mg, 1.735 mmol), palladium tetrakistriphenylphosphine (154.3 mg, 0.133 mmol), toluene (20 mL), ethanol (5 mL) and 2.0 M Na_2CO_3 (3.5 mL) afforded COMPOUND 45. The crude product was purified by flash column chromatography, eluting with EtOAc to give COMPOUND 45 as a pale yellow oil (630 mg, 95% yield). This oil was re-purified by reverse phase HPLC (gradient 10-60% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 45 (443 mg) as its TFA salt. This material was lyophilized from H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400MHz, $CDCl_3$) δ 0.90-1.37 (m, 6H), 1.91 (s, 3H), 2.38-2.97 (m, 4H), 3.09-3.71 (m, 8H), 4.45 (s, 2H), 7.17 (d, J = 8.01 Hz, 2H), 7.23-7.48 (m, 7H), 7.71 (s, 2H), 8.73 (s, 2H).

COMPOUND 46: 4-{[2-(acetylamino)phenyl][1-(pyridin-3-ylmethyl)piperidin-4-ylidene]methyl}-N,N-diethylbenzamide



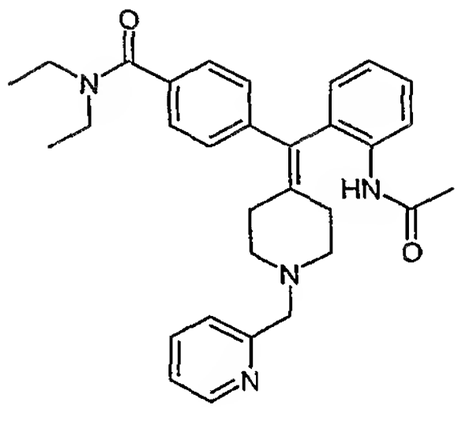
Using the same method as for COMPOUND 41 and using INTERMEDIATE 13 (590 mg, 1.33 mmol), 2-(acetylaminophenyl)boronic acid (310.6 mg, 1.735 mmol), palladium tetrakistriphenylphosphine (154.3 mg, 0.133 mmol), toluene (20 mL), ethanol (5 mL) and 2.0 M Na_2CO_3 (3.5 mL) afforded COMPOUND 46. The crude product was purified by reverse phase HPLC (gradient 10-40% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 46 (650 mg, 80% yield) as its TFA salt. This material was lyophilized from H_2O to produce a colorless solid. Purity (HPLC): > 96%; ^1H NMR (400MHz, $CDCl_3$) δ 1.02 (t, J = 6.44 Hz, 3H), 1.14 (t, J = 6.35 Hz, 3H), 1.83 (s, 3H), 3.10-3.28 (m, 10H), 3.35-3.52 (m, 2H), 4.37 (s, 2H), 7.07 (d, J = 7.42 Hz, 1H), 7.18-7.34 (m, 10H), 7.47-7.66 (m, 1H), 7.97 (d, J = 7.62 Hz, 1H). Found: C, 49.11; H, 4.53; N, 6.54. $C_{31}H_{36}N_4O_2$ x 3.5 $C_2HO_2F_3$ x 1.8 H_2O has C, 49.17; H, 4.68; N, 6.04%

COMPOUND 47: 4-[[2-(acetylamino)phenyl](1-butylpiperidin-4-ylidene)methyl]-N,N-diethylbenzamide



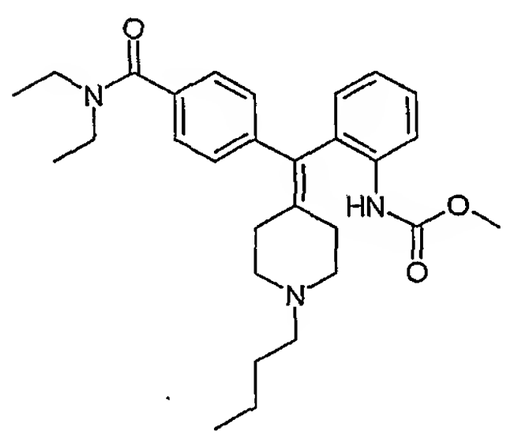
To a solution of COMPOUND 41 (500 mg, 1.19 mmol) and triethylamine (180 mg, 1.78 mmol) in dichloromethane (1 mL) was added acetyl chloride (110 μL, 1.54 mmol) at 0°C. The mixture was stirred overnight at room temperature. The solution was washed with H_2O. The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (2x). The combined organic phases was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by reverse phase HPLC (gradient 10-70% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 47 (267 mg, 49% yield) as its TFA salt. This material was lyophilized from H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400MHz, $CDCl_3$) δ 0.94-1.04 (m, 3H), 1.05-1.15 (m, 3H), 1.17-1.28 (m, 3H), 1.35-1.50 (m, 2H), 1.66-1.80 (m, 2H), 1.92 (d, J = 15.04 Hz, 3H), 2.31-2.78 (m, 2H), 2.82-3.20 (m, 3H), 3.21-3.35 (m, 5H), 3.44-3.75 (m, 4H), 7.09-7.22 (m, 2H), 7.27-7.39 (m, 6H). Found: C, 60.51; H, 6.50; N, 6.43. $C_{29}H_{39}N_3O_2$ x 1.5 $C_2HO_2F_3$ has C, 60.75; H, 6.45; N, 6.64%.

COMPOUND 48: 4-{[2-(acetylamino)phenyl][1-(pyridin-2-ylmethyl)piperidin-4-ylidene]methyl}-N,N-diethylbenzamide



Using the same method as for COMPOUND 47 and using COMPOUND 44 (502 mg, 1.10 mmol), acetyl chloride (95 mg, 1.21 mmol) and triethylamine (122.4 mg, 1.21 mmol) afforded COMPOUND 48 (111 mg, 20% yield) as its TFA salt. This material was lyophilized from H_2O to produce a colorless solid. Purity (HPLC): > 96%; ^{1}H NMR (400MHz, $CDCl_3$) δ 0.98-1.36 (m, 6H), 1.94 (s, 3H), 2.50-2.98 (m, 4H), 3.14-3.68 (m, 8H), 4.40-4.62 (m, 2H), 7.17 (d, J = 7.81 Hz, 2H), 7.24-7.40 (m, 7H), 7.41-7.56 (m, 2H), 7.90 (t. J = 7.71 Hz, 1H), 8.69 (d, J = 4.10 Hz, 1H). Found: C, 60.91; H, 5.54; N, 8.46. $C_{31}H_{36}N_4O_2$ x 1.5 $C_2HO_2F_3$ x 0.1 H_2O has C, 61.00; H, 5.68; N, 8.37%.

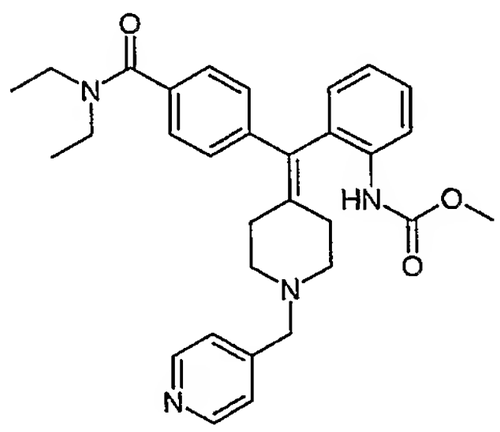
COMPOUND 49: methyl [2-((1-butylpiperidin-4-ylidene) {4[(diethylamino)carbonyl]phenyl}methyl)phenyl]carbamate



A mixture of zinc dust (17.4 mg, 0.267 mmol) and methyl chloroformate (41 μL, 0.534 mmol) in toluene (2 mL) was stirred for 1 hour at room temperature. A solution of COMPOUND 41 (112 mg, 0.267 mmol) in CH_2Cl_2 was added to the reaction dropwise. The reaction was stirred overnight at 80°C, diluted with CH_2Cl_2,

filtered and then washed with 1N $NaHCO_3$ (1x). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (1x). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by preparative thin layer chromatography with 1:1 EtOAc:Hexanes affording a colorless oil. This oil was re-purified by reverse phase HPLC (gradient 10-60% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 49 (26.3 mg, 17% yield) as its TFA salt. This material was lyophilized from H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400MHz, $CDCl_3$) δ 0.93-1.03 (m, 3H), 1.04-1.15 (m, 3H), 1.17-1.26 (m, 3H), 1.35-1.49 (m, 2H), 1.63-1.81 (m, 2H), 2.34-2.70 (m, 2H), 2.79-3.19 (m, 3H), 3.20-3.33 (m, 5H), 3.43-3.74 (m, 7H), 7.17-7.26 (m, 3H), 7.26-7.36 (m, 4H), 7.46 (dd, J = 33.4, 7.81 Hz, 1H). Found: C, 52.36; H, 5.77; N, 5.77. $C_{29}H_{39}N_3O_3$ x 2.7 $C_2HO_2F_3$ has C, 52.60; H, 5.35; N, 5.35%.

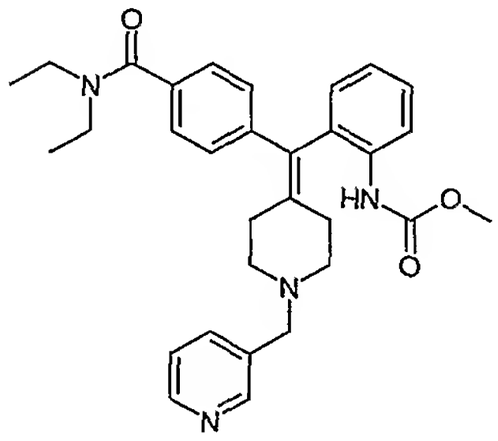
COMPOUND 50: methyl (2-{{4-[(diethylamino)carbonyl]phenyl}[1-(pyridin-4-ylmethyl)piperidin-4-ylidene]methyl}phenyl)carbamate



Using the same method as for COMPOUND 49 and using COMPOUND 42 (400 mg, 0.88 mmol), methyl chloroformate (166 mg, 1.76 mmol), and zinc dust (57.5 mg, 0.88 mmol) at 50°C afforded COMPOUND 50. The crude product was purified by flash column chromatography, eluting with 1:1 EtOAc/heptane to give COMPOUND 50 (282 mg, 62% yield). This compound was re-purified by reverse phase HPLC (gradient 10-60% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 50 as its TFA salt. This material was lyophilized from H_2O to

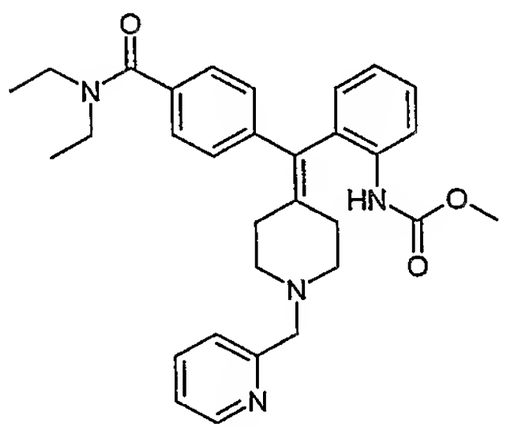
produce a colorless solid. Purity (HPLC): > 99%; ^{1}H NMR (400MHz, $CDCl_3$) δ 1.09 (t, J = 6.35 Hz, 3H), 1.16-1.30 (t, J = 5.76 Hz, 3H), 2.46-2.60 (m, 2H), 2.62-2.87 (m, 2H), 3.15-3.56 (m, 8H), 3.59 (s, 3H), 4.36-4.54 (m, 2H), 7.14-7.36 (m, 7H), 7.44 (d, J = 7.81 Hz, 1H), 7.72 (d, J = 4.49 Hz, 2H), 8.59-8.92 (m, 2H). Found: C, 54.48; H, 4.85; N, 7.95. $C_{31}H_{36}N_4O_3$ x 2.2 $C_2HO_2F_3$ x 0.80 H_2O has C, 54.66; H, 5.16; N, 7.20%.

COMPOUND 51: methyl (2-{{4-[(diethylamino)carbonyl]phenyl}[1-(pyridin-3-ylmethyl)piperidin-4-ylidene]methyl}phenyl)carbamate



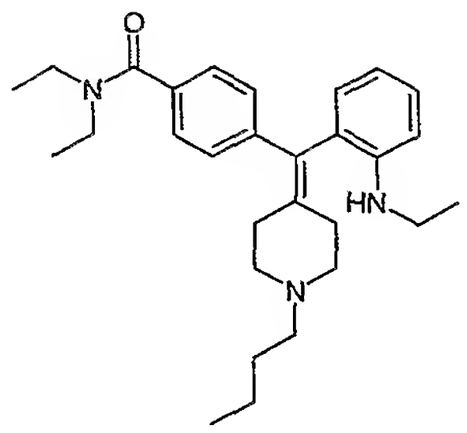
Using the same method as for COMPOUND 49 and using COMPOUND 43 (500 mg, 1.10 mmol), methyl chloroformate (208 mg, 2.20 mmol), and zinc dust (71.9 mg, 1.10 mmol) at 50°C afforded COMPOUND 51. The crude product was purified by reverse phase HPLC (gradient 10-50% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 51 as its TFA salt (335.4 mg, 59% yield). This material was lyophilized from H_2O to produce a colorless solid. Purity (HPLC): > 97%; ^{1}H NMR (400MHz, $CDCl_3$) δ 0.95-1.36 (m, 6H), 2.45-2.60 (m, 2H), 2.64-2.88 (m, 2H), 3.20-3.57 (m, 8H), 3.60 (s, 3H), 4.39-4.56 (m, 2H), 7.15-7.36 (m, 8H), 7.44 (d, J = 11.13 Hz, 1H), 7.62-7.76 (m, 1H), 8.16 (d, J = 7.62 Hz, 1H), 8.24 (s, 1H), 8.62-8.97 (m, 1H). Found: C, 56.77; H, 5.17; N, 7.73. $C_{31}H_{36}N_4O_3$ x 2.0 $C_2HO_2F_3$ has C, 56.76; H, 5.17; N, 7.56%.

COMPOUND 52: methyl (2-{{4-[(diethylamino)carbonyl]phenyl}[1-(pyridin-2-ylmethyl)piperidin-4-ylidene]methyl}phenyl)carbamate



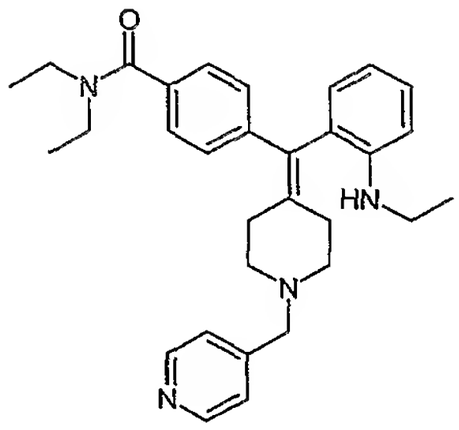
Using the same method as for COMPOUND 49 and using COMPOUND 44 (500 mg, 1.10 mmol), methyl chloroformate (208 mg, 2.20 mmol), and zinc dust (71.9 mg, 1.10 mmol) at 50°C afforded COMPOUND 52. The crude product was purified by flash column chromatography, eluting with 4:1 EtOAc/heptane to give COMPOUND 52 (156.7 mg, 28% yield). This compound was re-purified by reverse phase HPLC (gradient 10-60% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 52 (134 mg) as its TFA salt. This material was lyophilized from H_2O to produce a colorless solid. Purity (HPLC): > 97%; ^1H NMR (400MHz, $CDCl_3$) δ 1.10 (t, J = 8.00 Hz, 3H), 1.22 (t, J = 7.23 Hz, 3H), 2.59 (t, J = 6.05 Hz, 2H), 2.67-2.93 (m, 2H), 3.16-3.57 (m, 8H), 3.59-3.72 (m, 3H), 4.37-4.62 (m, 2H), 7.17-7.38 (m, 7H), 7.39-7.58 (m, 3H), 7.82-7.98 (m, 1H), 8.24 (s, 1H), 8.68 (d, J = 4.88 Hz, 1H). Found: C, 58.25; H, 5.72; N, 8.03. $C_{31}H_{36}N_4O_3$ x 1.5 $C_2HO_2F_3$ x 1.0 H_2O has C, 58.20; H, 5.67; N, 7.98%.

COMPOUND 53: 4-{(1-butylpiperidin-4-ylidene)[2-(ethylamino)phenyl]methyl}-N,N-diethylbenzamide



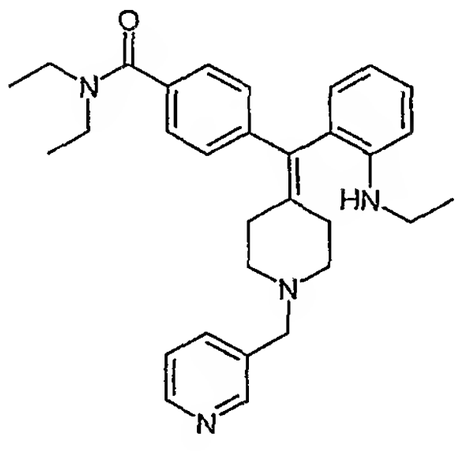
To a solution of COMPOUND 41 (190 mg, 0.452 mmol) and acetylaldehyde (20 mg, 0.452 mmol) in 1,2-dichoroethane (1 mL) was added $NaBH(OAc)_3$ (144 mg, 0.678 mmol) at rt. The reaction was stirred overnight at room temperature, washed with 2M NaOH solution (2x). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (2x). The combined organic phases was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 10-65% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 53 (100 mg, 48% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400 MHz, CD_3OD) δ 0.94-1.02 (m, 3H), 1.02-1.16 (m, 6H), 1.16-1.27 (m, 3H), 1.33-1.50 (m, 2H), 1.64-1.81 (m, 2H), 2.30-2.73 (m, 3H), 2.84-3.37 (m, 10H), 3.43-3.71 (m, 4H), 6.61-6.77 (m, 2H), 6.97 (dd, J = 62.58, 7.71 Hz, 1H), 7.16 (q, J = 7.88 Hz, 1H), 7.27-7.38 (m, 4H). Found: C, 62.90; H, 7.33; N, 6.99. $C_{29}H_{41}N_3O$ x 1.4 $C_2HO_2F_3$ has C, 62.89; H, 7.04; N, 6.92%.

COMPOUND 54: N,N-diethyl-4-{[2-(ethylamino)phenyl][1-(pyridin-4-ylmethyl)piperidin-4-ylidene]methyl}benzamide



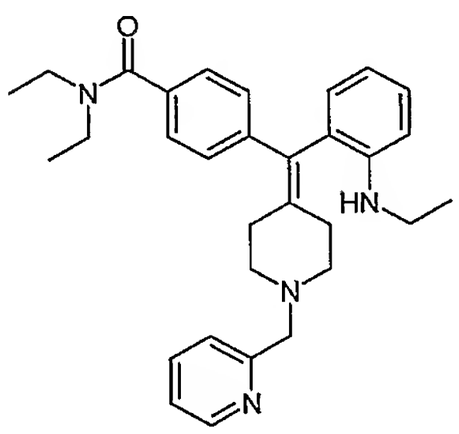
Using the same method as for COMPOUND 53 and using COMPOUND 42 (231.1 mg, 0.508 mmol), acetylaldehyde (22.4 mg, 0.508 mmol), and $NaBH(OAc)_3$ (161.6 mg, 0.763 mmol) afforded COMPOUND 54. The crude product was purified by reverse phase HPLC (gradient 10-40% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 54 (164.7 mg, 67% yield) as its TFA salt. This material was lyophilized from H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400MHz, $CDCl_3$) δ 1.02-1.16 (m, 6H), 1.23 (t, J = 6.54 Hz, 3H), 2.51 (t, J = 5.96 Hz, 2H), 2.71-2.89 (m, 2H), 2.93-3.05 (m, 1H), 3.07-3.20 (m, 1H), 3.21-3.61 (m, 9H), 4.37-4.53 (m, 2H), 6.71-6.88 (m, 2H), 7.04 (d, J = 6.83 Hz, 1H), 7.16-7.26 (m, 1H), 7.29-7.43 (m, 4H), 7.74 (d, J = 4.10 Hz, 2H), 8.56-9.00 (m, 2H). Found: C, 56.23; H, 5.56; N, 7.54. $C_{31}H_{38}N_4O$ x 2.30 $C_2HO_2F_3$ x 0.80 H_2O has C, 56.31; H, 5.56; N, 7.38%.

COMPOUND 55: N,N-diethyl-4-{[2-(ethylamino)phenyl][1-(pyridin-3-ylmethyl)piperidin-4-ylidene]methyl}benzamide



Using the same method as for COMPOUND 53 and using COMPOUND 43 (360 mg, 0.792 mmol), acetylaldehyde (34.9 mg, 0.792 mmol), and $NaBH(OAc)_3$ (251.8 mg, 1.18 mmol) afforded COMPOUND 55. The crude product was purified by reverse phase HPLC (gradient 10-60% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 55 (85 mg, 15% yield) as its TFA salt. This material was lyophilized from H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400MHz, $CDCl_3$) δ 1.03-1.14 (m, 6H), 1.23 (t, J = 6.93 Hz, 3H), 2.45-2.56 (m, 2H), 2.72-2.88 (m, 2H), 2.90-3.18 (m, 2H), 3.20-3.60 (m, 9H), 4.38-4.55 (m, 2H), 6.78-6.90 (m, 2H), 7.08 (d, J = 7.81 Hz, 1H), 7.19-7.27 (m, 1H), 7.30-7.40 (m, 5H), 7.62-7.79 (m, 1H), 8.16 (d, J = 7.81 Hz, 1H), 8.62-8.98 (m, 1H). Found: C, 55.54; H, 5.59; N, 7.51. $C_{31}H_{38}N_4O$ x 2.30 $C_2HO_2F_3$ x 1.40 H_2O has C, 55.52; H, 5.64; N, 7.27%.

COMPOUND 56: N,N-diethyl-4-{[2-(ethylamino)phenyl][1-(pyridin-2-ylmethyl)piperidin-4-ylidene]methyl}benzamide

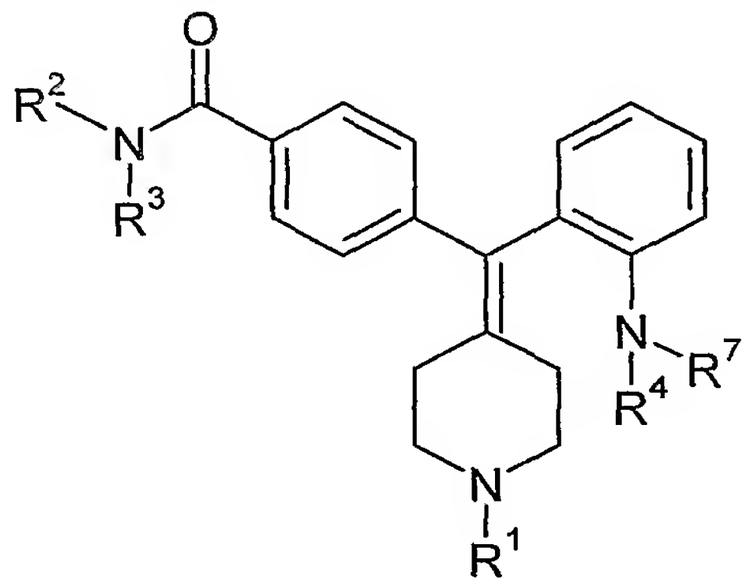


Using the same method as for COMPOUND 53 and using COMPOUND 44 (360 mg, 0.792 mmol), acetylaldehyde (34.9 mg, 0.792 mmol), and $NaBH(OAc)_3$ (251.8 mg, 1.18 mmol) afforded COMPOUND 56. The crude product was purified by reverse phase HPLC (gradient 10-60% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give COMPOUND 56 (220 mg, 39% yield) as its TFA salt. This material was lyophilized from H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^1H NMR (400MHz, $CDCl_3$) δ 1.04-1.16 (m, 6H), 1.23 (t, J = 6.54 Hz, 3H),

2.54 (t, J = 5.96 Hz, 2H), 2.73-2.93 (m, 2H), 2.97-3.21 (m, 2H), 3.21-3.61 (m, 9H), 4.50 (s, 2H), 6.70-6.84 (m, 2H), 7.02 (d, J = 7.62 Hz, 1H), 7.13-7.24 (m, 1H), 7.34 (s, 4H), 7.40-7.55 (m, 2H), 7.82-7.95 (m, 1H), 8.68 (d, J = 4.30 Hz, 1H). Found: C, 61.21; H, 6.22; N, 8.56. $C_{31}H_{38}N_4O$ x 1.5 $C_2HO_2F_3$ x 0.7 H_2O has C, 61.29; H, 6.19; N, 8.41%.

What is claimed is :

1. A compound of formula IA, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:



IA

wherein

R^1 is selected from hydrogen, C_{1-6}alkyl-O-C(=O)-, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{6-10}aryl, C_{2-9}heterocyclyl, C_{6-10}aryl-C_{1-3}alkyl and C_{2-9}heterocyclyl-C_{1-3}alkyl; wherein said C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{6-10}aryl, C_{2-9}heterocyclyl, C_{6-10}aryl-C_{1-3}alkyl and C_{2-9}heterocyclyl-C_{1-3}alkyl are optionally substituted with one or more groups selected from -R, $-NO_2$, -OR, -Cl, -Br, -I, -F, $-CF_3$, -C(=O)R, -C(=O)OH, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $-SO_3H$, $-SO_2R$, -S(=O)R, -CN, -OH, -C(=O)OR, $-C(=O)NR_2$, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen or C_{1-6}alkyl;

R^2, R^3 and R^4 are, independently, selected from hydrogen, C_{1-6}alkyl, and C_{3-6}cycloalkyl, wherein said C_{1-6}alkyl and C_{3-6}cycloalkyl are optionally substituted with one or more groups selected from -R, $-NO_2$, -OR, -Cl, -Br, -I, -F, $-CF_3$, -C(=O)R, -C(=O)OH, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $-SO_3H$, $-SO_2R$, -S(=O)R, -CN, -OH, -C(=O)OR, $-C(=O)NR_2$, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen or C_{1-6}alkyl; and

R^7 is selected from –H, -OH, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{6-10}aryl, C_{2-9}heterocyclyl, C_{6-10}aryl-C_{1-6}alkyl, C_{2-9}heterocyclyl-C_{1-6}alkyl, -C(=O)-NR^8R^9,

-C(=O)-O-R^8, –S(=O)-R^8, –S(=O)$_2$-R^8, -C(=O)-R^8 and -SO_3H, wherein R^8 and R^9 are independently selected from –H, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{6-10}aryl, C_{2-9}heterocyclyl, C_{6-10}aryl-C_{1-6}alkyl, and C_{2-9}heterocyclyl-C_{1-6}alkyl, wherein said C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{6-10}aryl, C_{2-9}heterocyclyl, C_{6-10}aryl-C_{1-6}alkyl, and C_{2-9}heterocyclyl-C_{1-6}alkyl used in defining R^7, R^8 or R^9 are optionally substituted with one or more groups selected from -R, -NO_2, -OR, -Cl, -Br, -I, -F, -CF_3, -C(=O)R, -C(=O)OH, -NH_2, -SH, -NHR, -NR_2, -SR, -SO_3H, -SO_2R, -S(=O)R, -CN, -OH, -C(=O)OR, -C(=O)NR_2, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen or C_{1-6}alkyl.

2. A compound according to claim 1,

wherein R^1 is selected from hydrogen, C_{1-6}alkyl-O-C(=O)-, C_{1-6}alkyl, C_{3-6}cycloalkyl, benzyl and C_{2-5}heteroarylmethyl, wherein said C_{1-6}alkyl, C_{3-6}cycloalkyl, benzyl and C_{2-5}heteroarylmethyl are optionally substituted with one or more groups selected from C_{1-6}alkyl, halogenated C_{1-6}alkyl, -CF_3, C_{1-6} alkoxy, chloro, fluoro, bromo, and iodo;

R^2 and R^3 are ethyl;

R^4 is selected from hydrogen and C_{1-3}alkyl;

R^7 is selected from –H, -OH, phenyl, C_{3-5}heterocyclyl, phenyl-C_{1-3}alkyl, C_{3-5}heterocyclyl-C_{1-3}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl-C_{1-3}alkyl, -C(=O)-N-R^8R^9, –C(=O)-O-R^8, –S(=O)-R^8, –S(=O)$_2$-R^8, -C(=O)-R^8 and -SO_3H, wherein R^8 and R^9 are independently selected from –H, phenyl, C_{3-5}heterocyclyl, phenyl-C_{1-3}alkyl, C_{3-5}heterocyclyl-C_{1-3}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl-C_{1-3}alkyl, wherein said phenyl, C_{3-5}heterocyclyl, phenyl-C_{1-3}alkyl, C_{3-5}heterocyclyl-C_{1-3}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl-C_{1-3}alkyl used in defining R^7, R^8 and R^9 are optionally substituted with one or more groups selected from C_{1-6}alkyl, halogenated C_{1-6}alkyl, -CF_3, C_{1-6} alkoxy, chloro, fluoro, bromo, and iodo.

3. A compound according to claim 1,

wherein R^1 is selected from hydrogen, C_{1-6}alkyl-O-C(=O)-, C_{1-6}alkyl, C_{3-6}cycloalkyl, benzyl, thiadiazolylmethyl, pyridylmethyl, thienylmethyl, furylmethyl, imidazolylmethyl, triazolylmethyl, pyrrolylmethyl, thiazolylmethyl and N-oxido-pyridylmethyl, wherein said C_{1-6}alkyl, C_{3-6}cycloalkyl, benzyl, thiadiazolylmethyl, pyridylmethyl, thienylmethyl, furylmethyl, imidazolylmethyl, triazolylmethyl, pyrrolylmethyl, thiazolylmethyl and N-oxido-pyridylmethyl are optionally substituted with one or more groups selected from C_{1-6}alkyl, halogenated C_{1-6}alkyl, -CF_3, C_{1-6} alkoxy, chloro, fluoro, bromo, and iodo;

R^2 and R^3 are ethyl;

R^4 is selected from hydrogen and methyl;

R^7 is selected from –H, C_{1-6}alkyl, phenyl-C_{1-3}alkyl, C_{3-7}cycloalkyl-C_{1-3}alkyl, C_{3-7}cycloalkyl, phenyl, C_{1-6}alkyl, -C(=O)-N-R^8R^9, –$S(=O)_2$-R^8, -C(=O)-O-R^8, and -C(=O)-R^8, wherein R^8 and R^9 are independantly selected from –H, phenyl-C_{1-3}alkyl, C_{3-7}cycloalkyl-C_{1-3}alkyl, C_{3-7}cycloalkyl, phenyl, and C_{1-6}alkyl, wherein said phenyl-C_{1-3}alkyl, C_{3-7}cycloalkyl-C_{1-3}alkyl, C_{3-7}cycloalkyl, phenyl, C_{1-6}alkyl used in defining R^7, R^8 and R^9 are optionally substituted with one or more groups selected from C_{1-6}alkyl, halogenated C_{1-6}alkyl, -CF_3, C_{1-6} alkoxy, chloro, fluoro, bromo, and iodo.

4. A compound according to claim 1,

wherein R^1 is selected from hydrogen, propyl, benzyl, thiadiazolylmethyl, pyridylmethyl, thienylmethyl, furylmethyl, imidazolylmethyl, triazolylmethyl, pyrrolylmethyl, thiazolylmethyl and N-oxido-pyridylmethyl;

R^2 and R^3 are ethyl;

R^4 is selected from hydrogen and methyl;

R^7 is selected from –H, ethyl, phenyl, benzyl or phenethyl, napthyl, fluorophenyl, chlorophenyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, cyclohexylmethyl, -C(=O)-NH-R^8, –$S(=O)_2$-R^8, -C(=O)-O-R^8, and -C(=O)-R^8, wherein R^8 is selected from methyl, 2,2,2-trifluoroethyl, phenyl, benzyl, phenethyl, methylphenyl, fluorophenyl, butyl, cyclohexyl and cyclohexylmethyl.

5. A compound according to claim 1, wherein the compound is selected from:

COMPOUND 1: 4-[[2-(benzoylamino)phenyl]-4-piperidinylidenemethyl]-*N*,*N*-diethylbenzamide;

COMPOUND 2: *N*-[2-[[4-[(diethylamino)carbonyl]phenyl]-4-piperidinylidenemethyl]phenyl]benzeneacetamide;

COMPOUND 3: 4-[[2-[(cyclohexylcarbonyl)amino]phenyl]-4-piperidinylidenemethyl]-*N*,*N*-diethylbenzamide;

COMPOUND 4: *N*-[2-[[4-[(diethylamino)carbonyl]phenyl]-4-piperidinylidenemethyl]phenyl]benzenepropanamide;

COMPOUND 5: 4-[[2-[(cyclohexylacetyl)amino]phenyl]-4-piperidinylidenemethyl]-*N*,*N*-diethylbenzamide;

COMPOUND 6: *N*,*N*-diethyl-4-[[2-[(2-phenylethyl)amino]phenyl]-4-piperidinylidenemethyl]benzamide;

COMPOUND 7: 4-[[2-[(cyclohexylmethyl)amino]phenyl]-4-piperidinylidenemethyl]-*N*,*N*-diethylbenzamide;

COMPOUND 8: *N*,*N*-diethyl-4-[[2-[(phenylmethyl)amino]phenyl]-4-piperidinylidenemethyl]-benzamide;

COMPOUND 9: 4-[[2-(cyclohexylamino)phenyl]-4-piperidinylidenemethyl]-*N*,*N*-diethylbenzamide;

COMPOUND 10: *N*,*N*-diethyl-4-[[2-[[(phenylamino)carbonyl]amino]phenyl]-4-piperidinylidenemethyl]benzamide;

COMPOUND 11: *N*,*N*-diethyl-4-[[2-(phenylamino)phenyl]-4-piperidinylidenemethyl]benzamide;

COMPOUND 12: *N*,*N*-diethyl-4-[[2-(methylphenylamino)phenyl]-4-piperidinylidenemethyl]benzamide;

COMPOUND 13: *N*,*N*-diethyl-4-[[2-[(phenylsulfonyl)amino]phenyl]-4-piperidinylidenemethyl]benzamide;

COMPOUND 14: *N,N*-diethyl-4-[[2-[[(phenylmethyl)sulfonyl]amino]phenyl]-4-piperidinylidenemethyl]benzamide;

COMPOUND 15: *N,N*-Diethyl-4-[4-piperidinylidene[2-[[(2,2,2-trifluoroethyl)sulfonyl]amino]phenyl]methyl]benzamide;

COMPOUND 16: 4-[{2-[(cyclopentylacetyl)amino]phenyl}(piperidin-4-ylidene)methyl]-*N,N*-diethylbenzamide;

COMPOUND 17: 4-[{2-[(cyclopentylcarbonyl)amino]phenyl}(piperidin-4-ylidene)methyl]-*N,N*-diethylbenzamide;

COMPOUND 18: *N,N*-diethyl-4-[{2-[(3-phenylpropyl)amino]phenyl}(piperidin-4-ylidene)methyl]benzamide;

COMPOUND 19: 4-[{2-[(2-cyclohexylethyl)amino]phenyl}(piperidin-4-ylidene)methyl]-*N,N*-diethylbenzamide;

COMPOUND 20: 4-[[2-(cyclopentylamino)phenyl](piperidin-4-ylidene)methyl]-*N,N*-diethylbenzamide;

COMPOUND 21: 4-[[2-(cycloheptylamino)phenyl](piperidin-4-ylidene)methyl]-*N,N*-diethylbenzamide;

COMPOUND 22: 4-[(2-{[(benzylamino)carbonyl]amino}phenyl)(piperidin-4-ylidene)methyl]-*N,N*-diethylbenzamide;

COMPOUND 23: *N,N*-diethyl-4-[[2-(1-naphthylamino)phenyl](piperidin-4-ylidene)methyl]benzamide;

COMPOUND 24: *N,N*-diethyl-4-[{2-[(3-fluorophenyl)amino]phenyl}(piperidin-4-ylidene)methyl]benzamide;

COMPOUND 25: 4-[{2-[(4-chlorophenyl)amino]phenyl}(piperidin-4-ylidene)methyl]-*N,N*-diethylbenzamide;

COMPOUND 26: 4-[{2-[cyclohexyl(methyl)amino]phenyl}(piperidin-4-ylidene)methyl]-*N,N*-diethylbenzamide;

COMPOUND 27: *N,N*-diethyl-4-[(2-{[(4-methylphenyl)sulfonyl]amino}phenyl)(piperidin-4-ylidene)methyl]benzamide;

COMPOUND 28: *N,N*-diethyl-4-[(2-{[(2-fluorophenyl)sulfonyl]amino}phenyl)(piperidin-4-ylidene)methyl]benzamide;

COMPOUND 29: 4-[{2-[(butylsulfonyl)amino]phenyl}(piperidin-4-ylidene)methyl]-*N,N*-diethylbenzamide;

COMPOUND 31: 4-[[2-(acetylamino)phenyl](piperidin-4-ylidene)methyl]-*N,N*-diethylbenzamide;

COMPOUND 32: methyl 2-[{4-[(diethylamino)carbonyl]phenyl}(piperidin-4-ylidene)methyl]phenylcarbamate;

COMPOUND 30: 4-[(2-aminophenyl)(1-benzylpiperidin-4-ylidene)methyl]-*N,N*-diethylbenzamide;

COMPOUND 33: 4-[[2-(acetylamino)phenyl](1-benzylpiperidin-4-ylidene)methyl]-*N,N*-diethylbenzamide;

COMPOUND 34: methyl 2-((1-benzylpiperidin-4-ylidene){4-[(diethylamino)carbonyl]phenyl}methyl)phenylcarbamate;

COMPOUND 35: 4-{(2-aminophenyl)[1-(1,3-thiazol-4-ylmethyl)piperidin-4-ylidene]methyl}-N,N-diethylbenzamide;

COMPOUND 36: 4-{(2-aminophenyl)[1-(1,3-thiazol-5-ylmethyl)piperidin-4-ylidene]methyl}-N,N-diethylbenzamide;

COMPOUND 37: 4-{[2-(acetylamino)phenyl][1-(1,3-thiazol-4-ylmethyl)piperidin-4-ylidene]methyl}-N,N-diethylbenzamide;

COMPOUND 38: methyl 2-{{4-[(diethylamino)carbonyl]phenyl}[1-(1,3-thiazol-4-ylmethyl)piperidin-4-ylidene]methyl}phenylcarbamate;

COMPOUND 39: 4-{[2-(acetylamino)phenyl][1-(1,3-thiazol-5-ylmethyl)piperidin-4-ylidene]methyl}-N,N-diethylbenzamide;

COMPOUND 40: methyl 2-{{4-[(diethylamino)carbonyl]phenyl}[1-(1,3-thiazol-5-ylmethyl)piperidin-4-ylidene]methyl}phenylcarbamate;

COMPOUND 41: 4-[(2-aminophenyl)(1-butylpiperidin-4-ylidene)methyl]-N,N-diethyl benzamide;

COMPOUND 42: 4-{(2-aminophenyl)[1-(pyridin-4-ylmethyl)piperidin-4-ylidene]methyl}-N,N-diethylbenzamide;

COMPOUND 43: 4-{(2-aminophenyl)[1-(pyridin-3-ylmethyl)piperidin-4-ylidene]methyl}-N,N-diethylbenzamide;

COMPOUND 44: 4-{(2-aminophenyl)[1-(pyridin-2-ylmethyl)piperidin-4-ylidene]methyl}-N,N-diethylbenzamide;

COMPOUND 45: 4-{[2-(acetylamino)phenyl][1-(pyridin-4-ylmethyl)piperidin-4-ylidene]methyl}-N,N-diethylbenzamide;

COMPOUND 46: 4-{[2-(acetylamino)phenyl][1-(pyridin-3-ylmethyl)piperidin-4-ylidene]methyl}-N,N-diethylbenzamide;

COMPOUND 47: 4-[[2-(acetylamino)phenyl](1-butylpiperidin-4-ylidene)methyl]-N,N-diethylbenzamide;

COMPOUND 48: 4-{[2-(acetylamino)phenyl][1-(pyridin-2-ylmethyl)piperidin-4-ylidene]methyl}-N,N-diethylbenzamide;

COMPOUND 49: methyl [2-((1-butylpiperidin-4-ylidene){4[(diethylamino)carbonyl]phenyl}methyl)phenyl]carbamate;

COMPOUND 50: methyl (2-{{4-[(diethylamino)carbonyl]phenyl}[1-(pyridin-4-ylmethyl)piperidin-4-ylidene]methyl}phenyl)carbamate;

COMPOUND 51: methyl (2-{{4-[(diethylamino)carbonyl]phenyl}[1-(pyridin-3-ylmethyl)piperidin-4-ylidene]methyl}phenyl)carbamate;

COMPOUND 52: methyl (2-{{4-[(diethylamino)carbonyl]phenyl}[1-(pyridin-2-ylmethyl)piperidin-4-ylidene]methyl}phenyl)carbamate;

COMPOUND 53: 4-{(1-butylpiperidin-4-ylidene)[2-(ethylamino)phenyl]methyl}-N,N-diethylbenzamide;

COMPOUND 54: N,N-diethyl-4-{[2-(ethylamino)phenyl][1-(pyridin-4-ylmethyl)piperidin-4-ylidene]methyl}benzamide;

COMPOUND 55: N,N-diethyl-4-{[2-(ethylamino)phenyl][1-(pyridin-3-ylmethyl)piperidin-4-ylidene]methyl}benzamide;

COMPOUND 56: N,N-diethyl-4-{[2-(ethylamino)phenyl][1-(pyridin-2-ylmethyl)piperidin-4-ylidene]methyl}benzamide;

and pharmaceutically acceptable salts thereof.

6. A compound according to any one of claims 1-5 for use as a medicament.

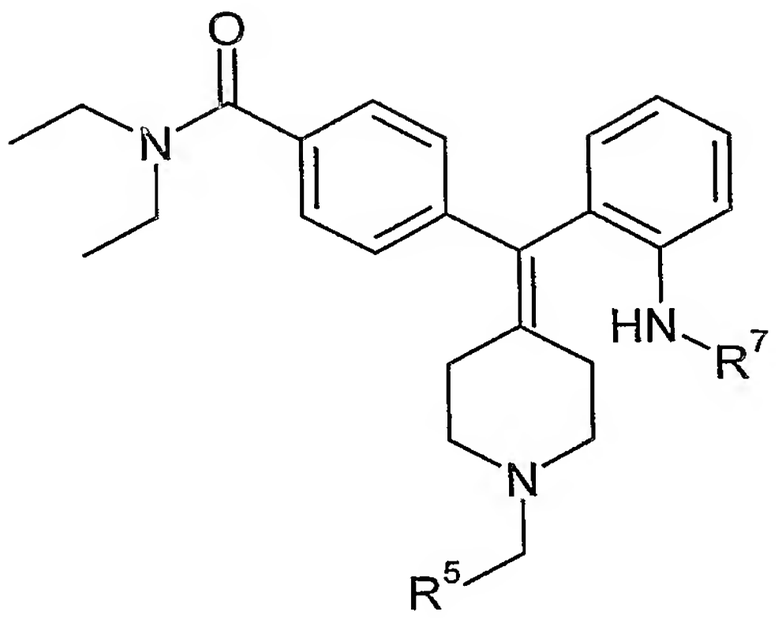
7. The use of a compound according to any one of claims 1-5 in the manufacture of a medicament for the therapy of pain, anxiety or functional gastrointestinal disorders.

8. A pharmaceutical composition comprising a compound according to any one of claims 1-5 and a pharmaceutically acceptable carrier.

9. A method for the therapy of pain in a warm-blooded animal, comprising the step of administering to said animal in need of such therapy a therapeutically effective amount of a compound according to any one of claims 1-5.

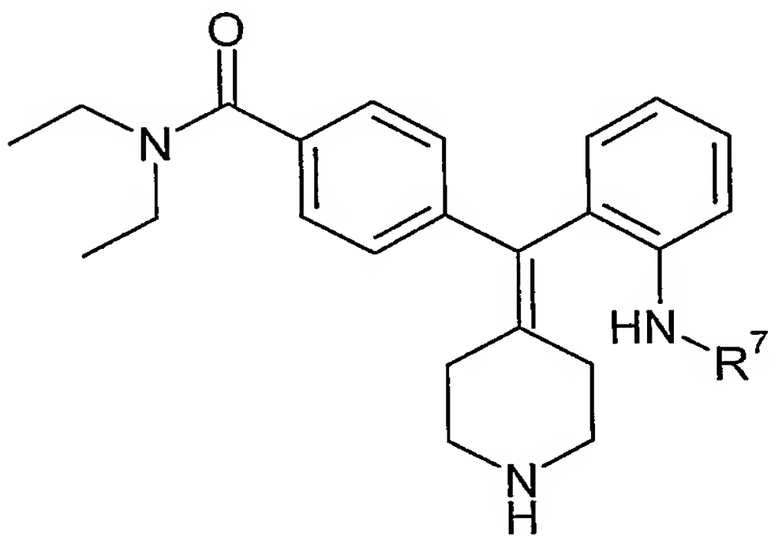
10. A method for the therapy of functional gastrointestinal disorders in a warm-blooded animal, comprising the step of administering to said animal in need of such therapy a therapeutically effective amount of a compound according to any one of claims 1-5.

11. A process for preparing a compound of formula IIA, comprising:



IIA

reacting a compound of formula IIIA with R^5-CH_2-X or R^5-CHO:



IIIA

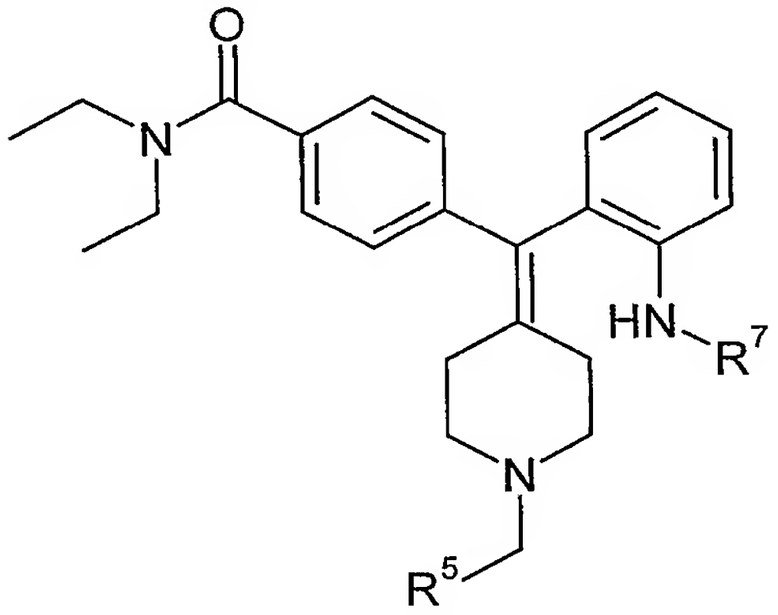
wherein X is a halogen;

R^7 is selected from –C(=O)-O-R^8, –S(=O)-R^8, –S(=O)$_2$-R^8, and -C(=O)-R^8,

wherein R^8 is selected from C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{6-10}aryl, C_{2-9}heterocyclyl, C_{6-10}aryl-C_{1-6}alkyl, and C_{2-9}heterocyclyl-C_{1-6}alkyl, wherein said C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{6-10}aryl, C_{2-9}heterocyclyl, C_{6-10}aryl-C_{1-6}alkyl, and C_{2-9}heterocyclyl-C_{1-6}alkyl are optionally substituted with one or more groups selected from -R, -NO_2, -OR, -Cl, -Br, -I, -F, -CF_3, -C(=O)R, -C(=O)OH, -NH_2, -SH, -NHR, -NR_2, -SR, -SO_3H, -SO_2R, -S(=O)R, -CN, -OH, -C(=O)OR, -C(=O)NR_2, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen or C_{1-6}alkyl; and

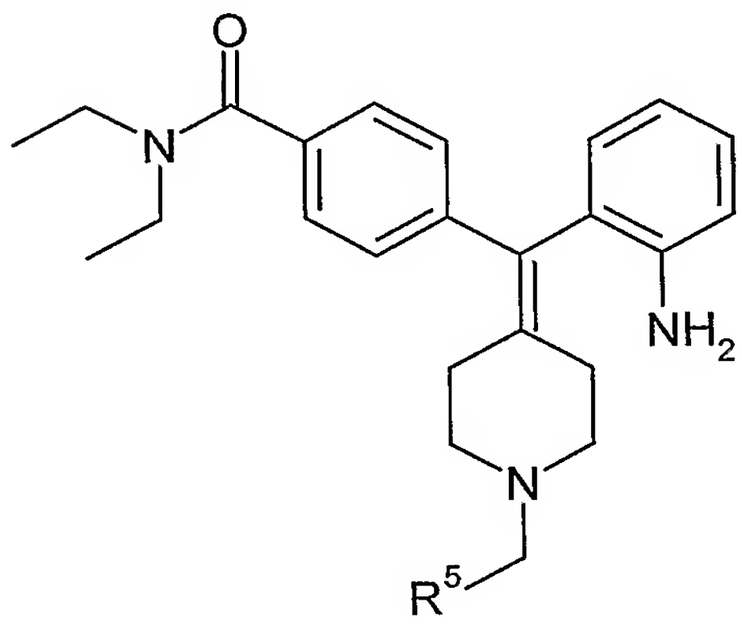
R^5 is selected from C_{6-10}aryl and C_{2-5}heteroaryl, wherein said C_{6-10}aryl and C_{2-5}heteroaryl are optionally substituted with one or more groups selected from -R, -NO_2, -OR, -Cl, -Br, -I, -F, -CF_3, -C(=O)R, -C(=O)OH, -NH_2, -SH, -NHR, -NR_2, -SR, -SO_3H, -SO_2R, -S(=O)R, -CN, -OH, -C(=O)OR, -C(=O)NR_2, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen or C_{1-6}alkyl.

12. A process for preparing a compound of formula IIA, comprising:



IIA

reacting a compound of formula IVA with R^7-X or R^7-O-R^7:



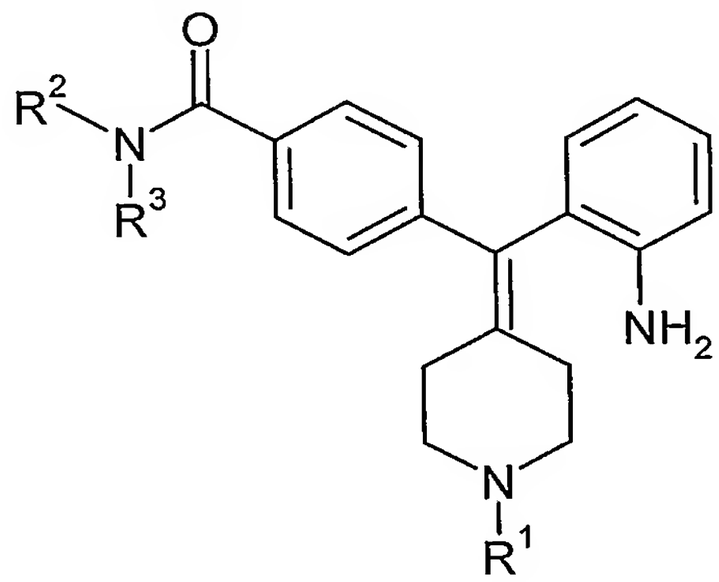
IVA

wherein X is a halogen;

R^7 is selected from –C(=O)-O-R^8 and -C(=O)-R^8, wherein R^8 is selected from C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{6-10}aryl, C_{2-9}heterocyclyl, C_{6-10}aryl-C_{1-6}alkyl, and C_{2-9}heterocyclyl-C_{1-6}alkyl, wherein said C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{6-10}aryl, C_{2-9}heterocyclyl, C_{6-10}aryl-C_{1-6}alkyl, and C_{2-9}heterocyclyl-C_{1-6}alkyl are optionally substituted with one or more groups selected from -R, $-NO_2$, -OR, -Cl, -Br, -I, -F, $-CF_3$, -C(=O)R, -C(=O)OH, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $-SO_3H$, $-SO_2R$, -S(=O)R, -CN, -OH, -C(=O)OR, $-C(=O)NR_2$, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen or C_{1-6}alkyl; and

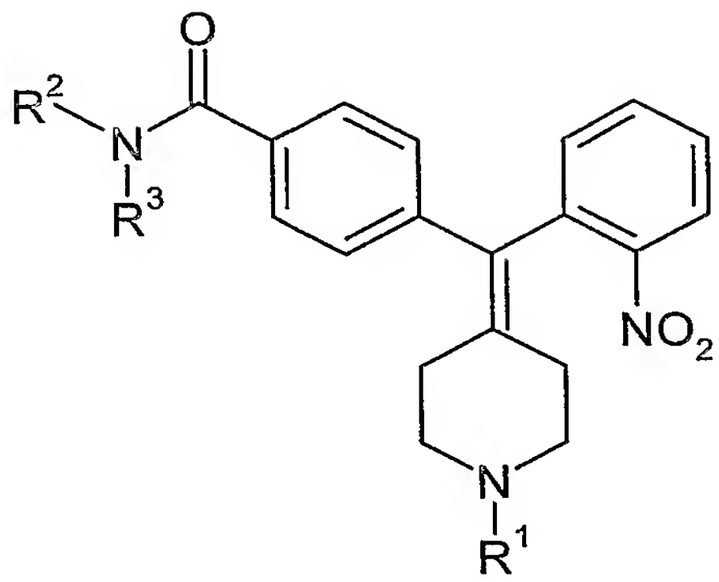
R^5 is selected from C_{6-10}aryl and C_{2-5}heteroaryl, wherein said C_{6-10}aryl and C_{2-5}heteroaryl are optionally substituted with one or more groups selected from -R, $-NO_2$, -OR, -Cl, -Br, -I, -F, $-CF_3$, -C(=O)R, -C(=O)OH, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $-SO_3H$, $-SO_2R$, -S(=O)R, -CN, -OH, -C(=O)OR, $-C(=O)NR_2$, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen or C_{1-6}alkyl.

13. A process of preparing a compound of formula VA,



VA

comprising reducing a compound of formula VIA,



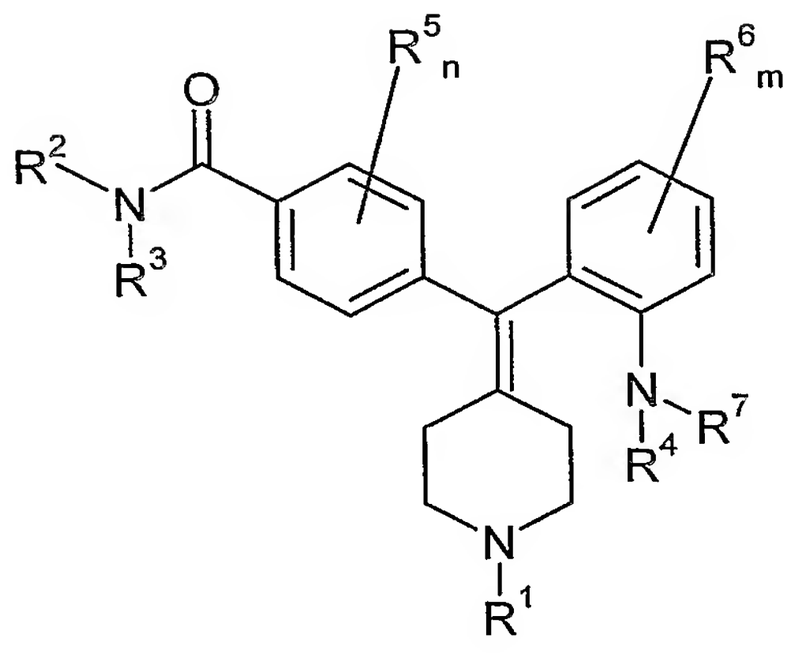
VIA

wherein

R^1 is selected from hydrogen, C_{1-6}alkyl-O-C(=O)-, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{6-10}aryl, C_{2-9}heterocyclyl, C_{6-10}aryl-C_{1-3}alkyl and C_{2-9}heterocyclyl-C_{1-3}alkyl; wherein said C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{6-10}aryl, C_{2-9}heterocyclyl, C_{6-10}aryl-C_{1-3}alkyl and C_{2-9}heterocyclyl-C_{1-3}alkyl are optionally substituted with one or more groups selected from -R, -NO_2, -OR, -Cl, -Br, -I, -F, -CF_3, -C(=O)R, -C(=O)OH, -NH_2, -SH, -NHR, -NR_2, -SR, -SO_3H, -SO_2R, -S(=O)R, -CN, -OH, -C(=O)OR, -C(=O)NR_2, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen or C_{1-6}alkyl; and

R^2 and R^3 are, independently, selected from hydrogen, C_{1-6}alkyl, and C_{3-6}cycloalkyl, wherein said C_{1-6}alkyl and C_{3-6}cycloalkyl are optionally substituted with one or more groups selected from -R, -NO_2, -OR, -Cl, -Br, -I, -F, -CF_3, -C(=O)R, -C(=O)OH, -NH_2, -SH, -NHR, -NR_2, -SR, -SO_3H, -SO_2R, -S(=O)R, -CN, -OH, -C(=O)OR, -C(=O)NR_2, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen or C_{1-6}alkyl.

14. A compound of formula I, a pharmaceutically acceptable salt thereof, diasteromers, enantiomers, or mixtures thereof:



I

wherein

R^1 is selected from hydrogen, C_{1-6}alkyl-O-C(=O)-, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted C_{6-10}aryl, optionally substituted C_{2-9}heterocyclyl, optionally substituted C_{6-10}aryl-C_{1-3}alkyl and optionally substituted C_{2-9}heterocyclyl-C_{1-3}alkyl;

n is 0, 1 or 2; m is 0, 1, or 2;

R^2, R^3 and R^4 are, independently, selected from hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-6}cycloalkyl;

R^5 and R^6 are, independently, selected from -R, $-NO_2$, -OR, -Cl, -Br, -I, -F, $-CF_3$, -C(=O)R, -C(=O)OH, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $-SO_3H$, $-SO_2R$, -S(=O)R, -CN, -OH, -C(=O)OR, $-C(=O)NR_2$, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen or C_{1-6}alkyl; and

R^7 is selected from –H, -OH, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted C_{6-10}aryl, optionally substituted C_{2-9}heterocyclyl, optionally substituted C_{6-10}aryl-C_{1-6}alkyl, optionally substituted C_{2-9}heterocyclyl-C_{1-6}alkyl, $-C(=O)-NR^8R^9$, $-C(=O)-O-R^8$, $-S(=O)-R^8$, $-S(=O)_2-R^8$, $-C(=O)-R^8$ and $-SO_3H$, wherein R^8 and R^9 are independently selected from –H, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-8}cycloalkyl, optionally

substituted C_{6-10}aryl, optionally substituted C_{2-9}heterocyclyl, optionally substituted C_{6-10}aryl-C_{1-6}alkyl, and optionally substituted C_{2-9}heterocyclyl-C_{1-6}alkyl.

15. A compound according to claim 14,

wherein R^1 is selected from hydrogen, C_{1-6}alkyl-O-C(=O)-, optionally substituted C_{1-6}alkyl, and optionally substituted C_{3-6}cycloalkyl;

R^2 and R^3 are ethyl;

R^4 is selected from hydrogen and C_{1-3}alkyl;

R^7 is selected from –H, -OH, optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl, optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted C_{3-6}cycloalkyl-C_{1-3}alkyl, -C(=O)-N-R^8R^9, –C(=O)-O-R^8, –S(=O)-R^8, –S(=O)$_2$-R^8, -C(=O)-R^8 and -SO_3H, wherein R^8 and R^9 are independently selected from –H, optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl, optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted C_{3-6}cycloalkyl-C_{1-3}alkyl; and

n and m are 0.

16. A compound according to claim 14,

wherein R^1 is selected from hydrogen and C_{1-6}alkyl-O-C(=O)-;

R^2 and R^3 are ethyl;

R^4 is selected from hydrogen and methyl;

R^7 is selected from –H, phenyl-C_{1-3}alkyl, C_{3-6}cycloalkyl-C_{1-3}alkyl, C_{3-6}cycloalkyl, phenyl, optionally substituted C_{1-6}alkyl, -C(=O)-N-R^8R^9, –S(=O)$_2$-R^8, and -C(=O)-R^8, wherein R^8 and R^9 are independantly selected from –H, phenyl-C_{1-3}alkyl, C_{3-6}cycloalkyl-C_{1-3}alkyl, C_{3-6}cycloalkyl, phenyl, and optionally substituted C_{1-6}alkyl; and

n and m are 0.

17. A compound according to claim 14, wherein

R^1 is hydrogen;

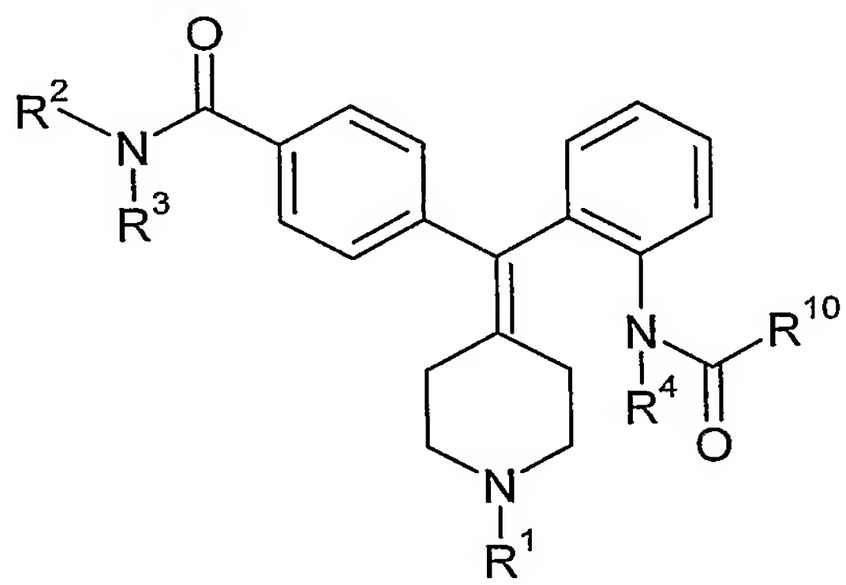
R^2 and R^3 are ethyl;

R^4 is selected from hydrogen and methyl;

R^7 is selected from –H, phenyl, benzyl or phenethyl, cyclohexyl, cyclohexylmethyl, -C(=O)-NH-R^8, –S(=O)$_2$-R^8, and -C(=O)-R^8, wherein R^8 is selected from 2,2,2-trifluoroethyl, phenyl, benzyl or phenethyl, cyclohexyl and cyclohexylmethyl; and

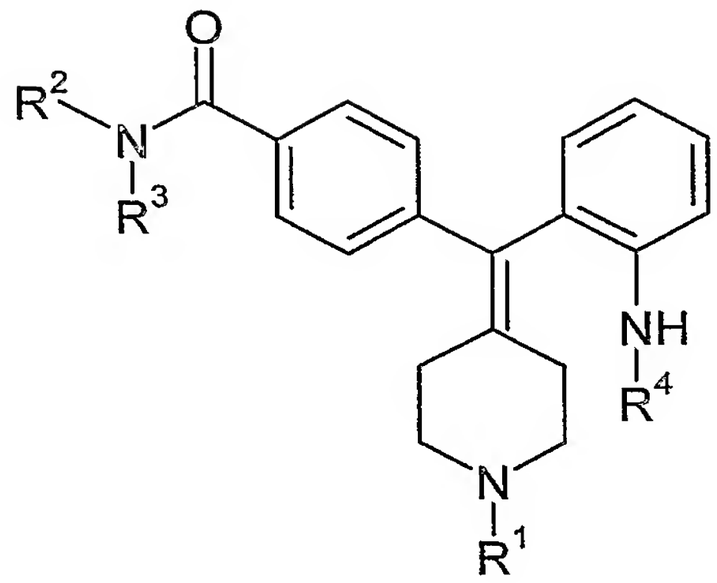
n and m are 0.

18. A process for preparing a compound of formula II, comprising:



II

reacting a compound of formula III with X^1-C(=O)-R^{10}:



III

wherein

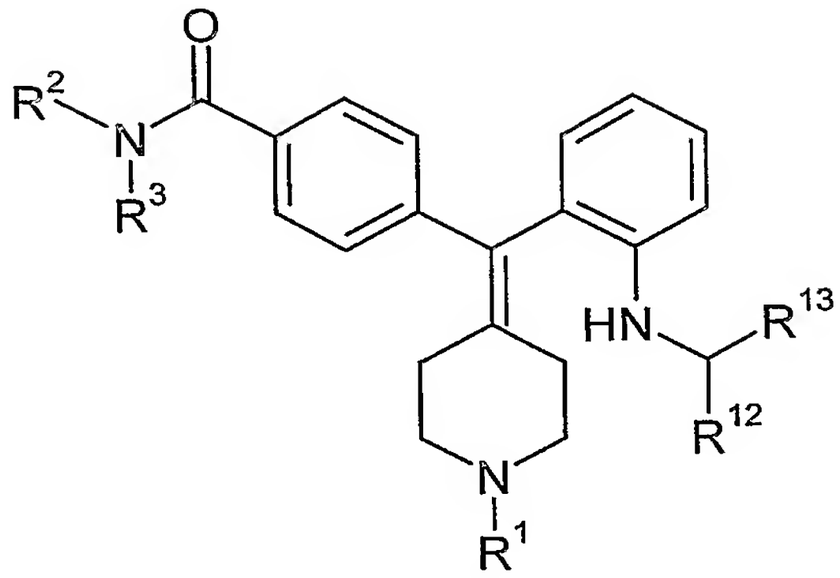
R^1 is selected from C_{1-6}alkyl-O-C(=O)-, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl and optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl;

X^1 is selected from –OH, -OR^{11}, -O-C(=O)-R^{11}, -Cl, -Br and -I, wherein R^{11} is C_{1-6}alkyl;

R^2, R^3 and R^4 are, independently, selected from hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-6}cycloalkyl; and

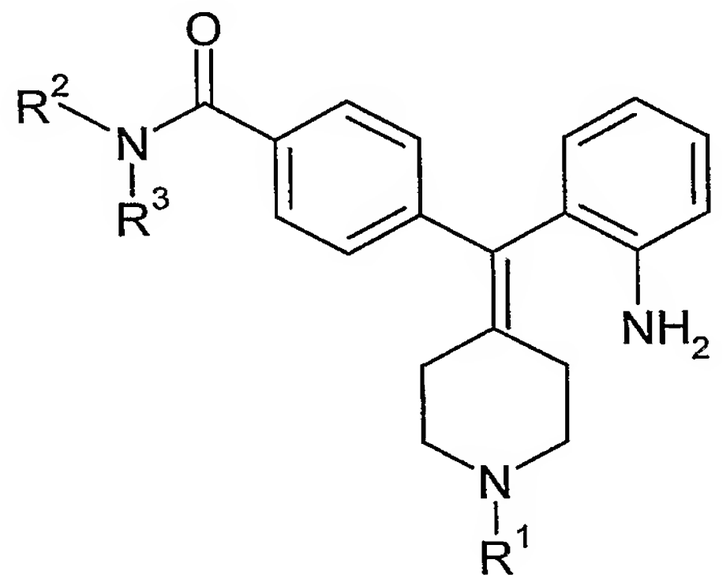
R^{10} is selected from –H, optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl, optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl and optionally substituted C_{3-6}cycloalkyl-C_{1-3}alkyl.

19. A process for preparing a compound of formula IV, comprising:



IV

reacting a compound of formula V with R^{12}-C(=O)-R^{13}:



V

wherein

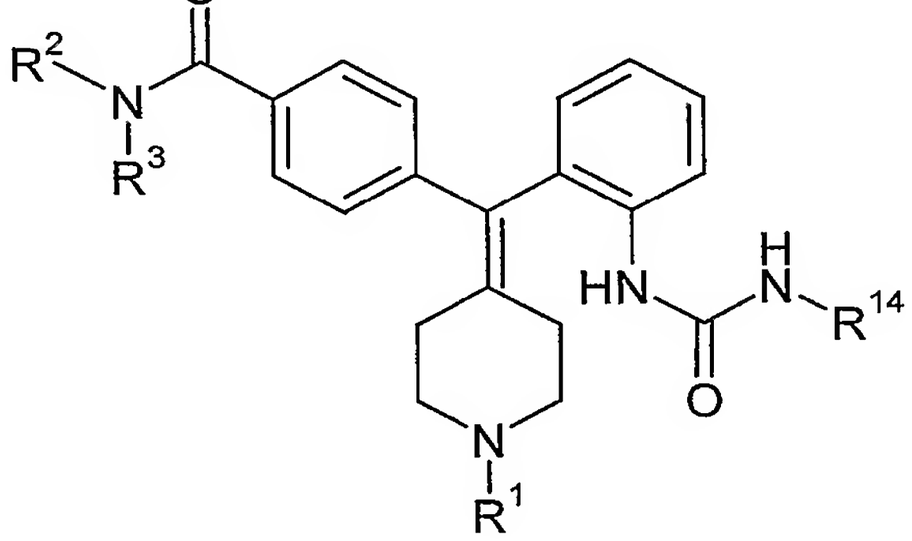
R^1 is selected from C_{1-6}alkyl-O-C(=O)-, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl and optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl;

R^2 and R^3 are, independently, selected from hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-6}cycloalkyl; and

R^{12} and R^{13} are independently selected from –H, optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl,

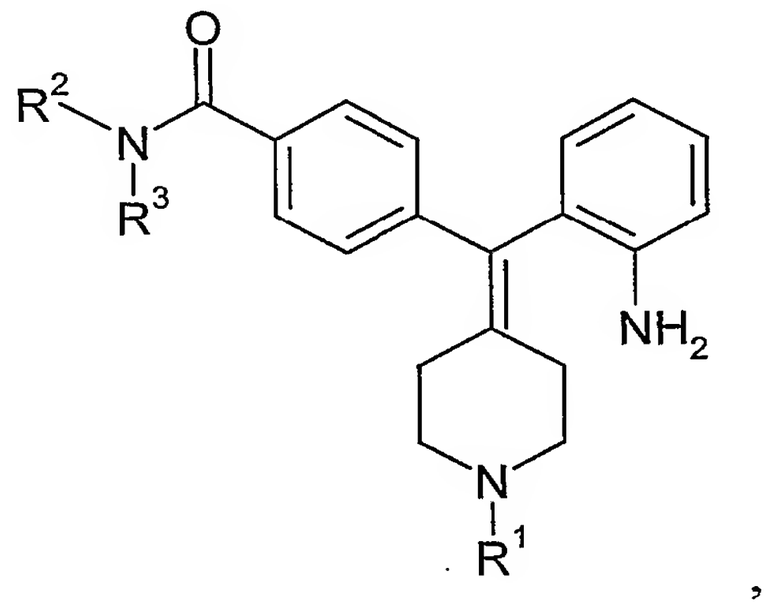
optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl and optionally substituted C_{3-6}cycloalkyl-C_{1-3}alkyl, or R^{12} and R^{13} together form a portion of a C_{3-6}cycloalkyl ring or a C_{3-5}heterocylcyl ring.

20. A process for preparing a compound of formula VI, comprising:



VI

reacting a compound of formula V with R^{14}-NCO:



V

wherein

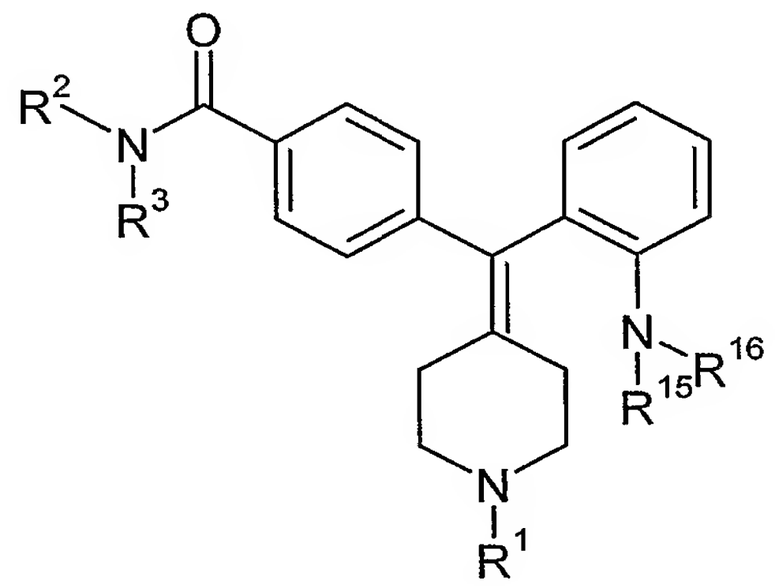
R^1 is selected from C_{1-6}alkyl-O-C(=O)-, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted phenyl, optionally

substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl and optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl;

R^2 and R^3 are, independently, selected from hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-6}cycloalkyl; and

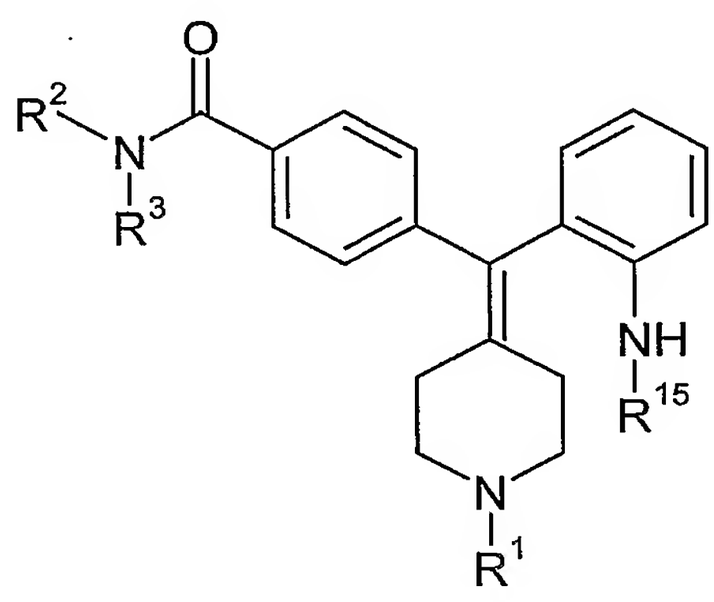
R^{14} is selected from optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl, optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl and optionally substituted C_{3-6}cycloalkyl-C_{1-3}alkyl.

21. A process for preparing a compound of formula VII, comprising:



VII

reacting a compound of formula VIII with R^{16}-X^2:



,

VIII

wherein

R^1 is selected from C_{1-6}alkyl-O-C(=O)-, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl and optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl;

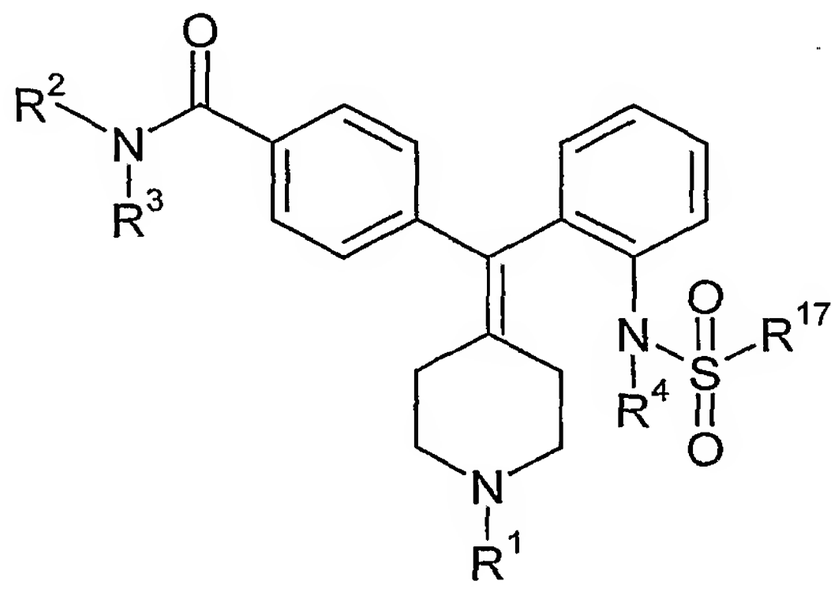
R^2 and R^3 are, independently, selected from hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-6}cycloalkyl;

X^2 is selected from I, Br and Cl;

R^{15} is selected from –H, optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl, optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl and optionally substituted C_{3-6}cycloalkyl-C_{1-3}alkyl; and

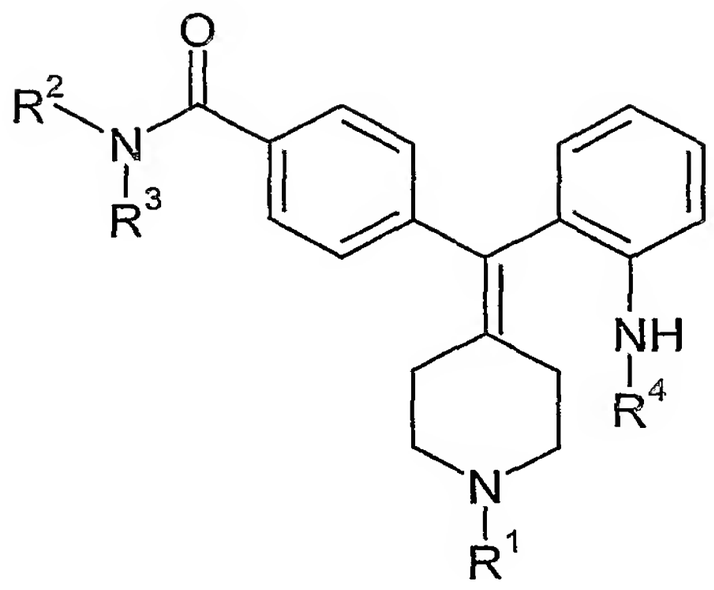
R^{16} is selected from optionally substituted phenyl-C_{1-3}alkyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl and optionally substituted C_{3-6}cycloalkyl-C_{1-3}alkyl.

22. A process for preparing a compound of formula IX, comprising:



IX

reacting a compound of formula III with X^3-S(=O)$_2$-R^{17}:



III

wherein

R^1 is selected from C_{1-6}alkyl-O-C(=O)-, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl and optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl;

X^3 is selected from –OH, -OR^{11}, -Cl, -Br and -I, wherein R^{11} is C_{1-6}alkyl;

R^2, R^3 and R^4 are, independently, selected from hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-6}cycloalkyl; and

R^{17} is selected from –H, optionally substituted phenyl, optionally substituted C_{3-5}heterocyclyl, optionally substituted phenyl-C_{1-3}alkyl, optionally substituted C_{3-5}heterocyclyl-C_{1-3}alkyl, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl and optionally substituted C_{3-6}cycloalkyl-C_{1-3}alkyl.

INTERNATIONAL SEARCH REPORT

International Application No
.../GB2004/002074

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/70 C07D417/06 C07D401/06 A61K31/435 A61K31/444
A61K31/4427 A61P25/04 A61P25/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 187 792 B1 (WEI ZHONGYONG ET AL) 13 February 2001 (2001-02-13) claims 1-4,8-10; example 42	1-22
Y	WO 02/094812 A (WALPOLE CHRISTOPHER ; BROWN WILLIAM (CA); ASTRAZENECA AB (SE)) 28 November 2002 (2002-11-28) claims 1,8-13	1-22
Y	WO 02/094786 A (WALPOLE CHRISTOPHER ; BROWN WILLIAM (CA); WEI ZHONGYONG (CA); ASTRAZEN) 28 November 2002 (2002-11-28) claims 1,8-13	1-22

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 October 2004	13/10/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	vanVoorsttotVoorst,M

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2004/002074

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 9,10
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9 and 10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

itional Application No
PCT/GB2004/002074

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